DESIGN AND DEVELOPMENT OF A NOVEL IMPLANTABLE PROSTHETIC VEIN VALVE

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DESIGN AND DEVELOPMENT OF A NOVEL IMPLANTABLE PROSTHETIC VEIN VALVE

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SUMMARY

Over seven million Americans suffer from Chronic Venous Insufficiency (CVI), a painful and debilitating disease that affects leg veins. Problems associated with CVI include varicose veins, bleeding, ulcerations, severe swelling, deep vein thrombosis, and pulmonary embolism, which may lead to death. The presence of CVI is the result of damaged one-way vein valves, or incompetent valves, in leg veins. When normally functioning, these valves allow forward flow of blood to the heart, and prevent pooling of blood at the feet due to gravitational forces. However, as vein valves degrade in older patients, incompetent valves allow reflux of blood, and cause clinical problems. There are few effective clinical therapies for treating CVI and certain treatments require the valve to be replaced. Vein valve transplants are surgical options for treatment. However, it is often difficult to find suitable donor valves within the same patient. Prosthetic valves have been developed in the past, but none have demonstrated sufficient clinical or mechanical functionality. Persistent problems include thrombus formation, valves that leak when backpressure is applied, and valves that do not open with a physiologic pressure gradient, which is typically less than 5 mmHg. The primary objective of this research was to develop a functional prosthetic vein valve for treating patients suffering from CVI. Additionally, this research proposes engineering design requirements for a prosthetic vein valve, and develops functional tests to assess a prosthetic valve's performance.

The novel prosthetic valve is flexible, biocompatible, has low thrombogenecity, and is easy to manufacture. It was designed to address well-defined consumer needs and functional design requirements. The valve was required to 1) withstand 300 mmHg of backpressure with less than 1.0 mL leakage per minute, 2) open with a pressure gradient less than 5 mmHg, and 3) meet criteria 1 and 2 even after 500,000 cycles of opening and closing in simulated physiologic conditions. Bench testing demonstrated that the valve met these three critical design requirements. The valve can open with pressure gradients as low as 2.0 ± 0.5 mmHg, and can withstand 300 mmHg with a leak-rate less than 0.3 mL/min. The valve remained functional even after opening and closing over 500,000 times. The valve burst at a pressure of 530 ± 10 mmHg, six times greater than physiologic pressure. The valve presented in this research is operationally functional, and shows good potential as a solution to treating deep valvular incompetence in CVI patients.

CHAPTER 1

INTRODUCTION

CLINICAL BACKGROUND

Chronic Venous Insufficiency

Over seven million Americans suffer from Chronic Venous Insufficiency (CVI), a painful and debilitating disease that affects the venous system of the lower extremities [1]. The presence of CVI is usually the result of incompetent, or malfunctioning, one-way valves in leg veins. Incompetent valves cause 80 to 90 percent of CVI cases involving venous reflux [2]. The one-way valves in leg veins are critical for proper circulation because they prevent blood from pooling at the feet due to the force of gravity. In normal physiology, the calf muscle contracts during leg movement and squeezes blood upward through the valves. Using this muscle action of the calf, sometimes referred to as the "peripheral heart," the body is able to overcome gravitational forces to maintain blood flow back to the heart. However, in pathologies involving CVI, the leg veins and valves do not maintain proper blood flow to the heart, leading to a host of clinical problems.

Problems associated with CVI include varicose veins, ulcerations, bleed, and swelling, as well as more severe cases involving Deep Vein Thrombosis (DVT) and Pulmonary Embolism, which usually leads to death. Over 300,000 patients in the U.S. are affected annually by DVT [3, 4], and the total cost for treating these patients is estimated over $2 billion per year [5]. CVI tends to affect older patients, and with a growing population of

the elderly in developed countries, the incidence of CVI is likely to increase proportionally.

Figure 1: Ulcerations (left) and varicose veins (right) caused by vein valve incompetence. Note the severe swelling of both legs, due to hypertensive conditions. Pictures obtained from http://www.gvg.org.uk/vvinfo.htm

Etiology of Chronic Venous Insufficiency

There are two processes by which CVI arises; one involves the aging process, the other involves formation of an obstruction that damages vein valves. Venous incompetence that is the result of natural aging is often referred to as primary incompetence, while secondary incompetence refers to pathologies involving obstruction or destruction of the valve.

Primary incompetence develops as the structural composition of veins change. In an aging vein wall, the intima thickens and elastin fibers and muscle layers become disorientated and disorganized. Elastic lamina within the intima becomes more fragmented, atrophic, thin, and irregular [6]. Reduced elastic lamina in aged veins makes it more vulnerable to high pressure-distention. As veins distend, valves also distend, to the point where the leaflets within the valve no longer meet in the lumen to seal properly.

Secondary incompetence occurs when vein valves are destroyed, with leaflets becoming adherent, folding over, and being absorbed into the vein wall [7]. The incidence of secondary incompetence has been reported as high as 95% in patients having ulcerations and deep venous reflux [8]. Valve damage often occurs due to thrombus formation [9]. The valve leaflet pockets are the primary region of thrombus formation [10]. Poor sealing of valves leads to regurgitation and turbulence of blood flow, as well as areas of stagnant blood flow, increasing the likelihood of thrombus formation. This thrombus growth can then lead to the destruction of the afflicted vein valve. The absence of one

vein valve results in additional pressure applied on the next valve distal to the missing valve, and the process of vein distention and valve destruction cascades down the leg.

Other processes that lead to valvular incompetence and CVI involve vascular trauma, tumor growth, and also thrombus formation unrelated to valvular abnormalities, such as Deep Vein Thrombosis (DVT). Patients with a history of DVT have over a 25-fold increase chance for developing CVI compared to patients without a history of DVT [11].

Vein Structure and Mechanics

Veins, like arteries, have three main layers comprising the vessel wall. The inner-most layer is in contact with blood, and is called the tunica intima. The intima is very thin and contains fragmented elastic media [6]. Surrounding the intima is the second layer, the tunica media. The media has three distinguishable layers, with the innermost layer containing longitudinal muscle fibers, interconnected with elastin fibrils and connective tissue. The middle layer contains wide bundles of smooth muscle cells (SMC's) in circular orientation separated by elastic fibrils. The outer later contains longitudinally-orientated muscle bundles and fibrous tissue. Surrounding the vein media is the adventitia, which contains connective tissue, nerve fibers, and vasa vasorum.

The compliance of veins is very different from the compliance of arteries. Arteries have low distensibilty at low intramural pressures, and continue to be distensible even at high pressures. However, veins are highly distensible at low pressures, and distention ceases when intramural pressure reaches approximately 50 mmHg, with diameter expansion

limited to 1.5 to 1.6 times the original vein diameter (Figure 2) [12, 13]. The arrangement of various elastin and collagen fibrils, as well as the different muscle structure of vein walls, all contribute to the unique mechanics of veins. It is paramount that any prosthetic vein valve design accommodates vein distensibility appropriately. A prosthetic valve that is flexible may be ideal valve for vein distensibility. Accommodating vein distension will help minimize trauma to the vein, improve comfort for the patient, and may reduce the risk of inflammation or thrombus formation in the immediate valve area.

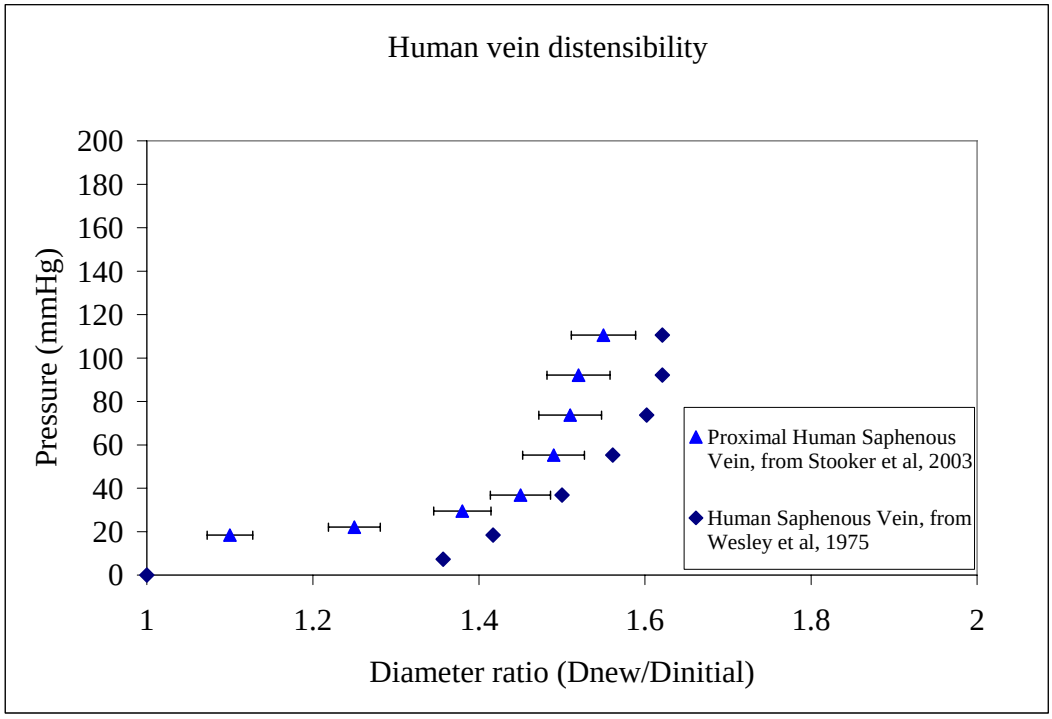


Figure 2: Human veins distend very easily at low pressure (less than 50 mmHg), and are limited in diameter expansion to 1.5 to 1.6 times their original diameter.

Vein Anatomy

In the legs, there are three venous networks that work in conjunction with each other to advance blood upwards to the heart. The deep venous system consists of veins of large diameter that lie deep underneath the muscles of the leg, close to the bones. The tibial vein is a deep vein found in the calf, which turns into the popliteal vein located just behind the knee. The popliteal vein then turns into the femoral vein which is located in the thigh, leading to the iliac vein and eventually the inferior vena cava. The superficial venous system consists of small diameter veins that are found just below the surface of the skin. Connecting the superficial veins to the deep veins are perforating veins. All of these vein systems contain one-way vein valves.

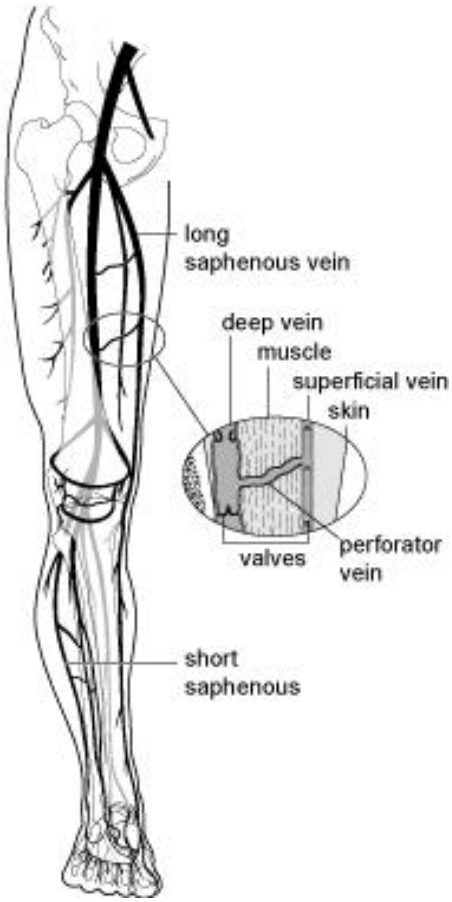


Figure 3: Venous anatomy of the leg. Diagram obtained from http://hcd2.bupa.co.uk/fact_sheets/html/Varicose_veins.html.

Table 1: Average occurrence of valves in deep veins [14]

Deep vein	**# of valves**
Common femoral vein (above sapheno-femoral junction)	1
Femoral vein (below sapheno-femoral junction)	3
Popliteal vein	1
Posterior tibial vein	19
Anterior tibial vein	11
Peroneal vein	10

There are two types of vein valves in legs: ostial valves and parietal valves. Ostial valves are positioned at the entry of a smaller vein branch into a larger vein, and aid in distribution of blood throughout the leg during leg muscle contractions. Parietal valves are generally positioned just proximal to a venous junction, within the larger vessel of the junction. Parietal valves are the main pressure-bearing valves, and are the more critical valves involved in CVI and surgical procedures.

Valve Function

Vein valves function by allowing antegrade (forward) blood flow to the right atrium of the heart, while preventing retrograde (reverse or reflux) flow to the feet. A functioning valve thus exhibits two very important characteristics: patency and competency. A valve that is patent remains open during antegrade flow, free of obstruction or occlusion. A valve that is competent seals appropriately during physiologic reflux, preventing backwards flow of blood. Figure 4 depicts the difference between a valve that is competent and patent and a valve that is incompetent and obstructed.

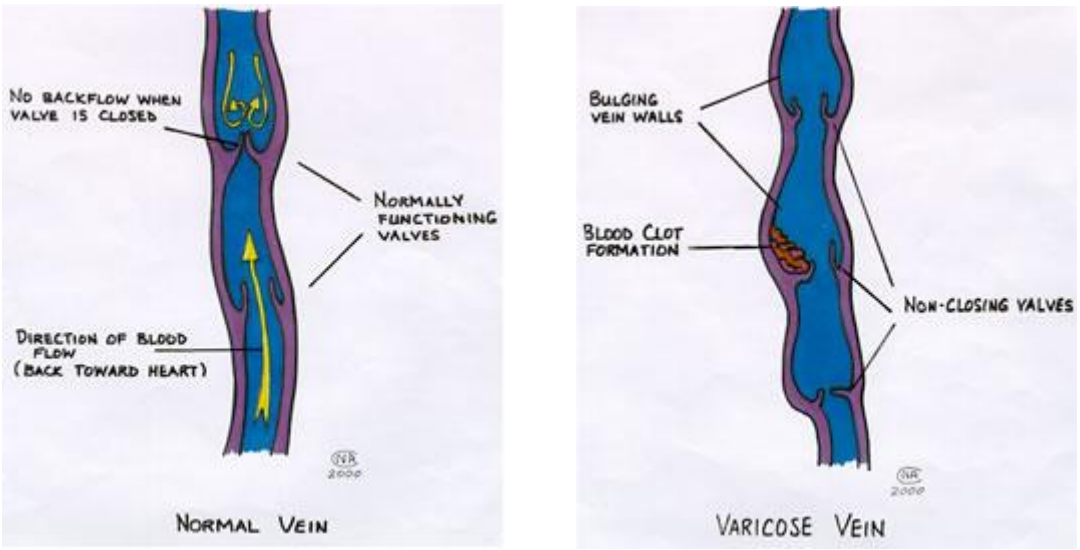


Figure 4: Competent and patent valves (left) and obstructed and incompetent valves (right). Diagrams obtained from http://www.veinexpert.com/vls-varicose_veins.htm.

Different vein valves open at different times through calf pump cycle [8]. During compression of the calf, deep vein valves open while valves in the perforating veins and valves distal to the location of muscle compression close. This synchronous opening and closing of valves channels blood not only towards the heart, but ensures blood is channeled to the deep veins [9]. During a regular walking cadence, the calf muscle pumps approximately 40 times a minute. Typically with each calf pump, the blood stroke volume is 10 to 20 mL [9].

It is important to note that vein valve function differs from heart valve function due to the different hemodynamic environment. Heart valves operate in high pressure, high flow environments, while vein valves experience a lower pressure, lower flow environment. Heart valve closure is driven primarily by flow, while vein valve closure is instigated by a drop in sinus pressure. The low flow environment in the venous system creates

opportunity for red thrombus to form. This imposes different challenges for an implanted medical device than the challenges normally faced in an arterial system.

Valve Anatomy

A native vein valve has several distinguishing features that play important roles in its function. Vein valves can have anywhere between one and five leaflets that coapt in the lumen of the vein to form a sealing valve. However, generally vein valves are bi-leaflet. The valve orifice is elliptic in nature, with an opening area about 35% of the full luminal area [15]. Veins tend to be elliptical in cross-section, due to the muscular pressure within the legs. Valve leaflets are also orientated such that longitudinal major axis follows the circumference of the deep fascial cross-section. Physiologic valves are capable of withstanding very high proximal pressure gradients with minimal leakage, and can open at very low distal pressure gradients. When a person is standing or sitting, the leg vein valves are open, allowing forward flow of blood. Thus venous pressure equals pressure from column of blood from point of measurement to right atrium of heart [16, 17]. However, when a person is or walking or suddenly stands from a sitting position, valves are opening and closing with each muscle movement.

Valve leaflets range in thickness from about 20 to 50 microns, and are composed of collagenous fibers covered with two unicellular endothelialized layers. One cell layer forms the parietal side, which faces proximally towards the valve sinus. The other cell layer faces the distal lumen. The parietal side contains some small ridges, while the luminal side of the leaflet is generally very smooth [14]. The commissure is the contact

point of the leaflets, and the region of each leaflet between the commissure and the vein wall is referred to as the cornua.

The leaflets are parabolic in shape, and connect to the vein wall via the valvular agger, a thickened protrusion of the vein wall. The agger acts as a stiffening collar to prevent excessive vein dilation at the site of the leaflets (Figure 5) [14]. This helps limit vein distension to the sinus region. The media of the vein wall in the sinus region is only 20 to 25% as thick as the media of the vein wall elsewhere [18]. This allows localized sinus expansion, key mechanism for helping the valve open and close correctly.

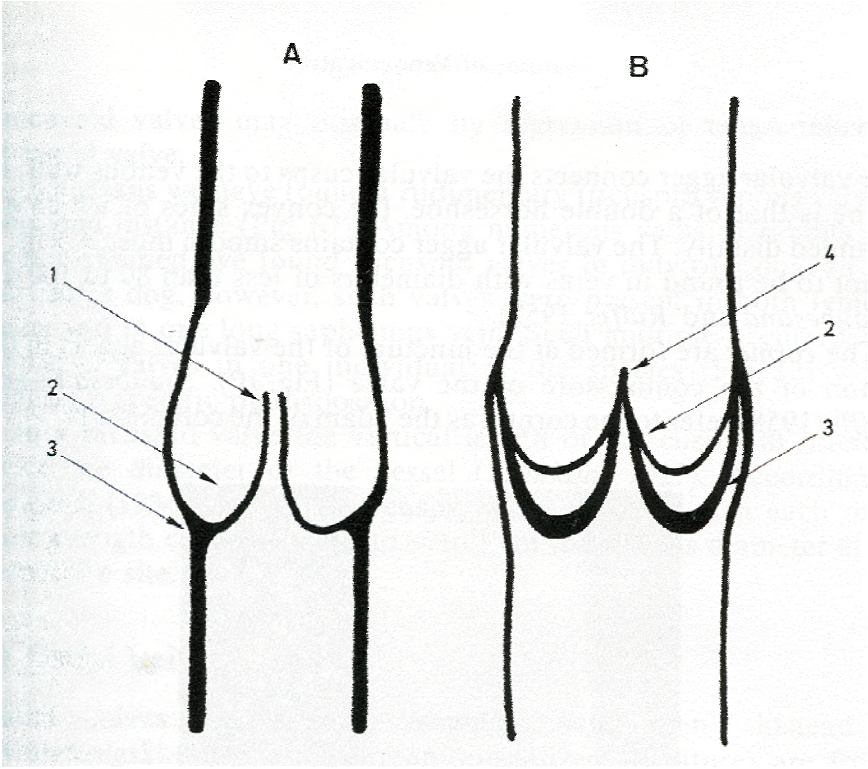


Figure 5: Anatomy of bi-leaflet vein valve [14]. 1) orifice 2) sinus pocket 3) valvular agger 4) valvular commissure

Valve Sinus and Vortical Flow

Recent studies have explored the importance of the sinus in the function of vein valves. When the valve is open, central axial flow goes through the orifice. Flow separation occurs at the leading edge of each of the leaflets, and reattaches at the walls of the sinus, creating a vortex in each sinus pocket. The streamlines of the vortex travel down the wall of the sinus, up the parietal side of the leaflet, and meet the central flow just proximal to the orifice (Figure 6).

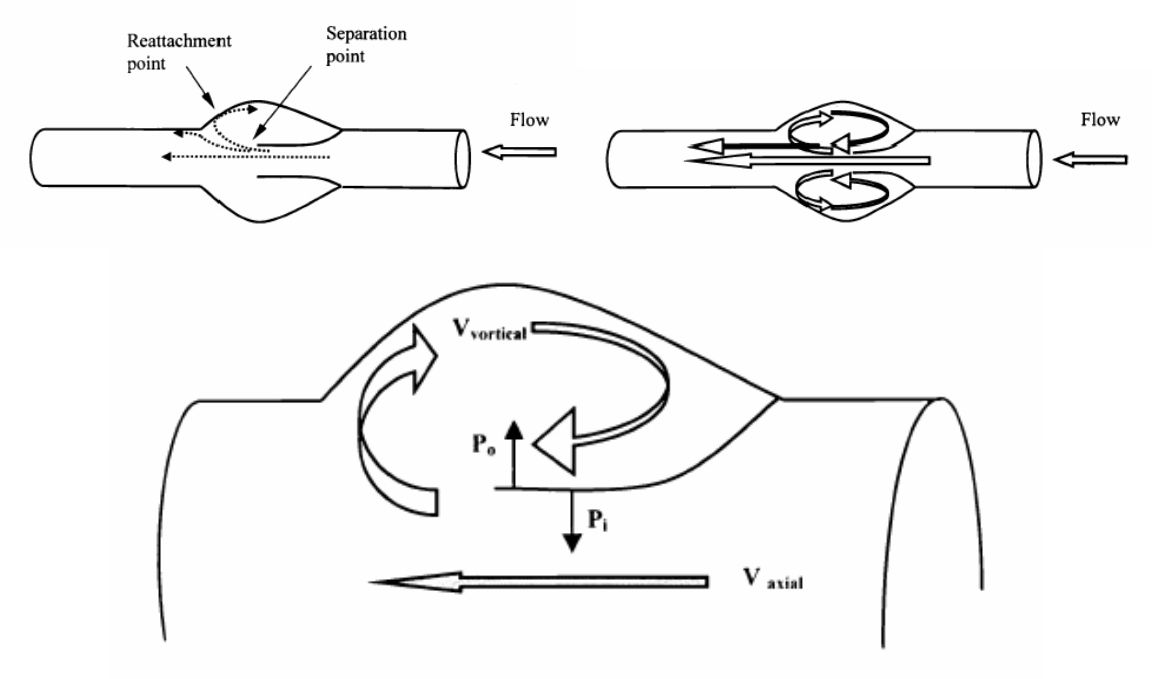


Figure 6: Vortical flow in valve sinus [15]

Vortical flow applies pressure on the parietal surface of cusps; when this pressure balances pressure on the luminal surface of the cusp, the valves remain open in equilibrium. Small perturbations in pressure, via muscle movement or changes in blood

flow, on either side of the cusp will cause oscillations of the leading edge of the cusps, while still in equilibrium [15].

Studies in the late 1980's and early 1990's led to the thought that reflux flow greater than 30 cm/s was required to close valves when subjects are in a supine position [19]. However, more recently, Lurie *et al* indicated that reverse flow is not necessary for valves to close, but rather that closure "coincides with the decrease of the flow velocities and the ballooning of the sinus." [20]. Results showed that reverse flow was absent through vein valves in 7 of 8 *in situ* cases. Valves responded to small negative pressure gradients, and closed before reflux occurred.

Lurie *et al* postulated that the ballooning of the sinus increased local pressure in the sinus due to decelerated flow. They noticed that the sinus bulged in size and became more spherical in shape, and that rotating flow in the sinus keeps cusps away from walls. Also, they observed that as antegrade flow slowed, the rotating flow in sinus slowed as well, and the pressure in the sinus started to close the valve before reflux could even occur [20].

Vortical flow is also thought to play an important role in preventing stasis of blood in the leaflet pockets, thus minimizing the potential of thrombus formation. Coupled with the pulsatility of venous flow from the calf muscle pump, vortical flow acts as a natural purging mechanism for removing cellular aggregates from the leaflet pockets [21]. This mechanism helps prevent blood stasis and keep normal valves free of thrombus formation.

Diagnosis of Venous Incompetence

Patients considered for vein valvuloplasty (valve repair) have symptoms of severe venous insufficiency and leg discomfort. Included amongst these symptoms are venous claudication, swelling, stasis dermatitis and ankle ulcerations [22]. Generally, the first phase of examination takes place in the office. After examining symptoms and patient history, the surgeon will determine if non-surgical management can be pursued or if additional tests are needed. Mild, uncomplicated varicose veins and telangiectasia (spider veins) can usually be treated without surgery [2]. If additional tests are needed, a non-invasive duplex ultrasound scan is usually the first vascular lab test conducted.

An ultrasound scan allows the surgeon to evaluate the more superficial veins of a patient. During duplex scanning, the surgeon attempts to elicit venous reflux response, and does so using one of several experiments, including cuff deflation, the valvalva maneuver, and manual calf compression in the standing position. Duplex scan shows sites of reflux and obstruction, and can help distinguish between superficial and deep problems [2]. Additional conventional ultrasound testing techniques include B-mode, color, and pulsed-wave Doppler scanning. The surgeon may ask the patient to perform the Valsalva maneuver, which entails the contraction of abdominal and upper leg muscles to induce higher venous pressure. The Valsalva maneuver accentuates venous problems, and is helpful for diagnosing incompetence at the more proximal vein valves. Finally, air plethysmography can be a useful method to determine obstruction and reflux; however,

generally, plethysmographic techniques are helpful only for determining presence and severity, but not location or causality, of incompetent valves.

After a patient is considered for a valvuloplasty or valve replacement, two tests are performed. First, an ascending venogram is conducted to map out veins in leg, showing location of deep, perforating, and superficial veins [2]. The ascending venogram usually involves injection of a contrast media in the dorsal foot vein. X-ray videography is used to image the flow of blood. This test is considered the gold-standard for demonstrating in vivo patency of a valve.

Secondly, a descending venogram will be performed to show the location of affected valves. A descending venogram is considered the gold-standard for detecting deep vein thrombosis and incompetent valves of the deep veins. For this venogram, contrast media is injected proximal to valve sites suspected to be damaged. The descending venogram is about 90% accurate in differentiating primary from secondary incompetence [2]. Valves affected by primary incompetence will leak media through the leaflets, while valves affected by secondary incompetence allow full flow of media downwards (Figure 7). It is important to differentiate the type of venous valve incompetence, as each type calls for different strategies of treatment. Primary venous incompetence can be surgically corrected via a valvuloplasty. It is much more difficult to correct secondary venous incompetence with surgery, mainly since the valves are destroyed beyond repair. The subsequent section titled “Current Clinical Therapy and Treatment” will discuss options for treating both primary and secondary incompetence.

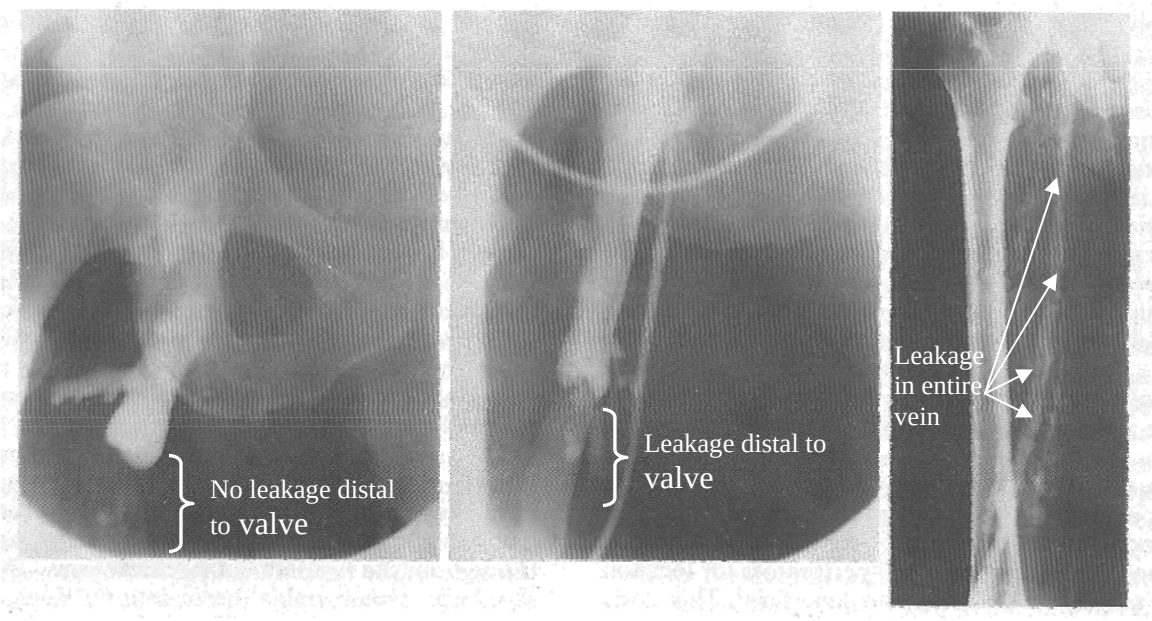


Figure 7: Descending venograms of common femoral vein by Kistner *et al* [2]. Left picture shows fully competent valve, preventing contrast agent from flowing below valve. Middle pictures shows valve having primary incompetence, where the valve cusps aren't sealing properly, evidenced by the leakage of contrast media distal (below) the valve site. Right picture shows entire post-thrombotic common femoral vein afflicted with secondary incompetence. Note that the contrast agent is found throughout the entire vein, indicating valves are destroyed.

Current Clinical Therapy and Treatment

There are few effective clinical therapies for treating CVI. Anti-coagulants, compressive hosiery, and bed-rest are non-invasive therapies that are typically used to help alleviate symptoms. However, these therapies can be very frustrating for the patient, particularly since bed-rest and compressive hosiery constrain a patient's lifestyle. Also, these therapies target the symptoms of CVI, rather than rectifying the cause of CVI.

There are several surgical options for treatment, depending on the severity and complexity of CVI in the patient. For patients suffering from superficial venous

incompetence, the affected veins can be stripped out. Blood flow will collateralize into the remaining functional superficial veins, and will generally not adversely affect the patient. This is a fairly common procedure, and can be done with minimally invasive techniques. If perforating veins are incompetent, they generally need to be interrupted to isolate their incompetence [2]. Interruption is achieved by ligating (tying off) the veins with sutures.

Surgical treatment for deep venous incompetence is a more complicated affair. The superficial and perforating venous systems have multiple vessels that will collateralize blood flow in the event a vessel is interrupted or removed. However, the deep veins are the main conduits of blood, and to remove or interrupt the deep veins is to essentially block blood from returning to the heart. Because the deep veins must remain in the body, another surgical approach must be taken.

Surgical treatment of the deep vein valves is dependent on the type of venous incompetence, primary or secondary competence, that afflicts the patient. Primary incompetence results in general widening of the valve commissural angle and elongation of the valve leaflets, meaning the valve leaflets are not coapting properly. Various surgical techniques can treat primary incompetence effectively because although the leaflets are deformed, the basic structure of the valve is intact [9]. This is evidenced by Ferris *et al* reported that after 4 years in femoral vein valve reconstruction patients, 70% of valve repairs were classified as “good or excellent” [23]. Surgical techniques used in such repairs include internal, external, and transcommissural valvuloplasty [24].

Valvuloplasty involves the strategic placement of several interrupted sutures where the valve leaflets join the vein wall, to help restructure the valve leaflets to their original anatomy.

Secondary incompetence appears more commonly in patients than primary incompetence [9]. Since often paired with thrombus formation, secondary incompetence results in the destruction of valve leaflets [9]. In the deep venous system, the most common cause of reflux is post-thrombotic valve damage. Some medical centers have reported as high as 95 percent of patients with venous ulceration and deep reflux having post-thrombotic valve damage [8]. Venous reflux due to secondary incompetence is rarely surgically repaired, and when it is, the repair seldom lasts [2]. Effective treatment for secondary valvular incompetence requires that the valves be replaced.

Valve Replacement

There are two main options in deep venous valve replacement: 1) transplantation or transposition and 2) prosthetic implantation. Taheri *et al* reported the first autologous vein valve transplant in a human patient in 1982 [25]. Transplantation is still used only in necessary cases, only after medication, physical rest and therapy, and other less invasive surgical procedures have been tried or considered. Valve transplant or transposition can cause unnecessary trauma to the patient's leg, and most procedures require indefinite post-operative anti-coagulation. Problems arise even prior to surgery because it is difficult to find a suitable donor valve. Since CVI is a systemic disease, the leg contralateral to the affected leg is usually afflicted with CVI as well. Thus the

probability of finding a functional autologous donor valve in the contralateral leg is low. This is evidenced by the fact that 30 to 40% of axillary vein valves, which are often used for superficial femoral venous valve replacement, are found incompetent prior to harvesting [26]. One study showed that transplanted and transposed valves had long term patency rates of 37-100% and 17-66%, respectively [27]. Despite these complications and risks, autologous vein valve transplant is generally considered the most effective treatment for secondary valvular incompetence of the deep veins.

In more recent years, a variety of mechanical and bioprosthetic implantable valves have been created and studied. However, few have demonstrated clinical potential for humans, with most valves revealing problems of poor patency due to thrombotic occlusions and elicited immunogenic response. In 1985, Hill *et al* reported designing an implantable venous valve similar to that of human anatomy. Some valves were fabricated of Pellethane®, a polyurethane elastomer, while others were fabricated of gluteraldehyde-fixed umbilical cord segments. Flow testing showed the valves opened with an applied pressure gradient of 4.5 mmHg. Eight days after implantation in dogs, all implanted valves had occluded due to red thrombus formation [28].

Also in 1985, Gerlock *et al* attempted using bioprosthetic cardiac valves as vein valves. Four gluteraldehyde-fixed pericardium annulus trileaflet valves coupled with Dacron® grafts were implanted into four dogs. Ascending venograms revealed patency in all four valves at six months [29]. However, valve competency or opening pressure results were not published.

Other research efforts have concentrated on designing mechanical vein valves. In 1988, Taheri *et al* developed a bi-leaflet mechanical valve design. They performed both *in vitro* and canine *in vivo* experiments on platinum and pyrolitic carbon-covered titanium valves [30]. After 16 weeks, six of ten valves remained patent and competent. Those valves that failed resulted in animal death or severe thrombotic occlusion. After two years, the valves were observed to induce severe intimal hyperplasia, which caused the valves to be functionless.

In 1993, DeLaria *et al* studied bovine jugular vein valves as potential replacements for deep venous valves in humans [31]. They studied the performance of both fresh and gluteraldehyde-fixed vein valves with respect to reflux and opening pressure. Fresh valves allowed a high leak-rate of 120 mL/min at an applied proximal pressure of 287 mmHg, and fixed valves allowed a leak-rate of 40 mL/min at the same proximal pressure. The study reported that fixed valves opened at 1 mmHg, although the leaflets were fixed in the open position to begin with.

Attempts at using cryopreserved human vein valves have also been pursued. However, Neglen and Raju reported in 2003 that cryopreserved venous valve allografts resulted in "high morbidity, high occlusion rate, poor patency, and poor clinical results." They found nearly three-fourths of the cryopreserved valves required some transcommissural repair prior to implantation. Thus, cryopreserved valves are not an effective option. The poor performance of cryopreserved valves was attributed to the effects of

cryopreservation on structural integrity and the immunogenic response elicited after implantation [32].

Between 2001 and 2003, Pavcnik *et al* reported making a vein valve prosthesis for transcatheter delivery. The valve comprised of nitinol wires and a sheath of porcine small intestine submucosa, an acellular material derived from porcine small intestines [33]. Twenty-five valves were implanted into sheep external jugular veins; 88% of the valves demonstrated good long term patency and competency [34]. The valves did show the ability to withstand 300 mmHg of backpressure, although leak-rate was not reported. However, these valves were tested against backpressure in a rigid tube; natural veins distend by 50% of diameter at high pressures, and it is more physiologically relevant to apply high proximal pressures in a vein-like environment. The opening pressure gradient for the valve was 1 mmHg. Valves that were placed incorrectly in the veins or tilted during deployment resulted in decreased function (12% of all valves), and 4% of all valves had thrombus formation [34, 35]. Curved veins and skewing had caused problems for the valve's functionality. While showing promise as a prosthetic vein valve, this valve may not be most appropriate for implantation into tortuous curvature of diseased veins. Little has been reported on the valve's durability and functionality after repeatedly opening and closing.

Table 2: Summary of current clinical therapies

Clinical Therapy	Purpose	Disadvantages
Anti-coagulation medication	Prevent DVT	Thins blood
Bed rest, elevated feet	Reduce pressure in lower leg	Prevents active lifestyle
Compressive hosiery	Reduces pressure in lower leg	Annoying for the patient
Sclerotherapy	Cosmetic procedure to treat spider veins	Useful only for superficial veins
Vein stripping	Removal of afflicted superficial veins	Removes blood vessels
Vein valve transplant	Replace damaged deep vein valves	Donor valves rarely available Often requires follow-up surgery Invasive operation

Table 3: Summary of prosthetic valve replacement studies in animals or humans

Investigator(s)	Valve type	Outcome	Failure mechanisms
Hill, Schmidt et al (1985)	Pellethane® (canine model)	Occlusion of all 10 valves after 8 days	Poor patency
Hill, Schmidt et al (1985)	Gluteraldehyde-fixed umbilical cord segments (Canine model)	Occlusion of all 10 valves after 3 days; Valves opened at 4.5 mmHg	Poor patency
Gerlock et al (1985)	Cardiac bioprosthetic valves (bovine pericardium) (canine model)	Valves patent after 6 months; No competency assessment; No pressure testing	Immunogenic response in humans; Opening pressure unknown
Taheri et al 1988	Bi-leaflet mechanical valves (canine model)	40% valve implants resulted in thrombotic occlusion or animal death at 16 weeks	Poor patency; Erosion of valve through vein
DeLaria et al 1993	Bovine jugular vein valves (*in vitro* study)	Opening pressure less than 10 mmHg; 120 mL/min leak-rate for fresh valves; 40 mL/min leak-rate for gluteraldehyde-fixed valves	Poor long term competency (leak-rate is high); Immunogenic response in humans
Pavcnik et al (2001-2003)	SIS valve with nitinol (ovine model)	88% long-term patency and competency. No data on cyclic life. Thrombus formation for valves in tortuous anatomy or tilted positions.	Poor performance in pathological tortuous veins
Neglen and Raju (2003)	Cryo-preserved human valves (human trial)	"High morbidity, high occlusion rate, poor patency, and poor clinical results."	Poor patency; Poor competency

There are currently no commercially available prosthetic vein valves. Work is continuing to address key problems of preventing thrombus formation and immunogenic response, evidenced by the progress by Pavcnik *et al*. However, there remain many challenges, particularly in demonstrating cyclic life functionality in a vein-like environment. Also, the prosthetic valves should be biocompatible and should not elicit an immunogenic response. Thus, the material selected for the valve should be one that has demonstrated low thrombogenicity as well as low immunogenic response and is preferably in use in FDA-cleared medical devices. Finally, unlike prosthetic heart valves, test methods have not been well-established for evaluating a prosthetic vein valve. It is important for the research community to establish test methods for a venous valve, and to utilize design controls when creating a functional prosthetic vein valve.

SPECIFIC AIMS

1) Define clinically relevant design requirements for a prosthetic vein valve

The first goal of this research is to define a set of critical engineering design requirements that will serve as the driving factors in designing a prosthetic vein valve. Little work has been done to methodically define comprehensive design requirements. This research will use design methods to translate consumer needs into functional requirements, and create design criteria that a valve's performance can be measured against.

2) Develop relevant functional tests for assessing vein valve performance

A second goal of this research is to develop tests that can be used to appropriately assess a vein valve's functionality with respect to key design criteria. There has been little work done to define functional testing of vein valves, and this research proposes methodologies for functional testing. The tests will mimic human venous physiology, and will yield quantifiable and meaningful metrics that can be used to evaluate valve performance.

3) Design and manufacture a clinically relevant functional prosthetic vein valve

The primary goal of this research is to develop a novel prosthetic vein valve that can meet specified design requirements by undergoing functional testing. Thus, concentration will be placed on creating a prosthetic valve that is biocompatible, hemocompatible, easy to manufacture, easy to implant, and has a reasonable and achievable path to FDA-clearance. The valve will be designed to maximize patient benefit and reduce patient risk.

MARKET ANALYSIS

Market Overview

Nearly 1 million new CVI patients arise each year in the United States alone. About 40% of CVI patients have deep vein valve incompetence [36, 37]. Some medical centers have reported as high as 95% of patients that exhibited deep venous reflux having post-thrombotic damaged valves [8]. It is these patients suffering from secondary incompetence that are the most likely candidates for valve replacement. However, the small percentage of patients having primary incompetence in the deep veins could also be potential candidates for a prosthetic valve. Thus, the potential consumer base for a prosthetic vein valve is about 400,000 CVI patients per year. Assuming the prosthetic valve can be packaged into a stent-catheter delivery system for minimally invasive delivery, the total product price will be about $1000 dollars. This pricing is based on existing vascular interventional products that utilize stent and catheter systems. The multiplication of the price and potential patient population yields the estimated market size. Thus, the estimated U.S. market size for this device is approximately $400 million per year.

This is an untapped niche market; there is a distinct and urgent demand by vascular surgeons and patients for a medical device that can treat CVI effectively. The market size is likely to grow proportional to the rate of the growing elderly population.

Patient Profile

The majority of the patient population suffering from CVI is elderly. However, people who spend much of their day standing and even some pregnant women are also susceptible to CVI. Symptoms of incompetent deep vein valves include severe pain, infection, swelling, and ulcerations. A descending venogram will discern the presence of primary or secondary incompetence. The clinician can then determine if the benefit of implanting a prosthetic vein valve outweighs any potential risks associated with the surgery or device.

The average patient has painful aches in the thigh or leg is often present, that recede only after the patient sits for 15 or 20 minutes. Swelling begins after the patient gets out of bed in the morning. Swelling continues to the point where shoes cannot be worn, and it becomes difficult to walk because of heaviness in the leg. The quality of life is detrimentally affected – the patient cannot have an active lifestyle and is often instructed to remain in bed to prevent swelling. A patient's leg can have an unpleasant odor due to stasis dermatitis and ulcerations allowing bacteria to fester and rot the flesh. It can be embarrassing for the patient to be in social situations when their legs smell. Thus, the patient not only suffers physically, but emotionally and mentally as well. Patients are in great need of a clinical treatment that affords them improved health and quality of life. A functional prosthetic vein valve can address this unmet need.

Existing Technology

Currently, there are no prosthetic vein valves commercially available in the United States. Although this is a smaller market compared to coronary stents and Implantable Cardioverter Defibrillators, several companies are pursuing positions in the market. There are approximately twenty-five issued patents concerning prosthetic vein valves. Table 4 contains the U.S. patents that are displayed by the U.S. Patent and Trade Office's (USPTO) website when using a simple search with keywords "vein valve" or "venous valve."

Table 4: Prior patents issued by USPTO involving vein valves

U.S. Patent Number	Inventor(s)	Date of Issue
4851001	Taheri.	Jul., 1989
4904254 / 5147389	Lane.	Sep., 1992
5358518	Camilli.	Oct., 1994
5500014	Quijano et al.	Mar., 1996
5607465	Camilli	Mar., 1997
5824061	Quijano et al.	Oct., 1998
6287334	Moll et al.	Sep., 2001
6299637	Shaolian et al.	Oct., 2001
6315793	Bokros et al.	Nov., 2001
6319281	Patel.	Nov., 2001
6494909	Greenhalgh.	Dec., 2002
6503272	Duerig et al.	Jan., 2003
6562069	Cai et al.	May, 2003
6585761	Taheri.	Jul., 2003
6602286	Strecker	Aug, 2003
6652578	Bailey et al.	Nov. 2003
6676698	McGuckin, Jr. et al.	Jan., 2004
6695878	McGuckin, Jr. et al.	Feb., 2004
6705585	Roy.	Mar., 2004
6716241	Wilder et al.	Apr., 2004
6752828	Thornton.	Jun., 2004
6840957	DiMatteo et al.	Jan., 2005

While there are various prosthetic vein valve designs that have been pursued in the past, many have shortcomings that prevent them from being sufficiently functional designs. Many valve designs contain rigid elements that can impose stress concentrations on the vein wall. The following text describes the patented designs that are most similar to the invention presented in this thesis. A comparison of these relevant patents to the invention of this research shows that this novel implantable prosthetic vein valve does not infringe on other patents.

U.S. Patent 6,840,957, issued to DiMatteo *et al* on January 11, 2005 ("DiMatteo") describes an implantable prosthetic valve comprising a radially self-expanding collapsible scaffold that supports collapsible leaf valves. A radial expansion device, particularly one containing will place localized stresses on the vessel wall, potentially affecting the biological integrity of the vessel. If the expanded scaffold diameter is anything less than the maximum distended vein diameter, the scaffold may lose retention. However, if the valve diameter is larger than the maximum vein diameter, during vein collapse at low pressures there will be high stress concentrations in the vein wall. Multiple cycles of collapse and distention can lead to vein wall fatigue and damage.

DiMatteo *et al* also describes that the leaflets are formed with a metal framework, and the leaflets have a spring bias to either the open position or the closed position. A spring bias towards the closed position could impede the valve opening at sufficiently low pressure gradients. A spring bias towards the open position may not seal appropriately during reflux. Also, the leaf valves are described to be in abutting edge-to-edge contact. Line

contact sealing may pose risks in sealing appropriately when the valve exposed to a dynamic and tortuous anatomy, which is present in the venous system. A more robust form of sealing in the venous system would entail a surface contact seal.

US Patent 6,716,241, issued to Wilder *et al* on April 6, 2004, describes a valve with three parabolic lobes. The valve has uniform elasticity and is fully flexible, making it easily deformable under muscular pressure and contractions. However, a valve that deforms too easily may not be durable or robust in sealing. Also, a valve with three lobes must contend with the elliptical cross-section of natural veins as well as muscular contractions. Muscle contracts may impose non-uniform stress and strain on the valve's lobes, potentially causing them to fatigue at uneven rates.

US Patent 6,494,909, issued to Greenhalgh on December 17, 2002, describes a radially expandable tube constructed of braided intermeshed filaments containing leaflets that are flexibly biased inwards. Thus the leaflets are inhomogenously elastic. Inwardly biased leaflets create additional resistance to antegrade flow. In that situation, there is a risk that normal physiologic pressure gradients may not be able to open the valve, causing an obstruction of blood flow.

Other references describe valves incorporating a rigid stent or support structure, such as the valve described by US Patent 6,562,069, issued to Cai, *et al*, on May 13, 2003. The invention describes a valve for cardiac use which has an open orifice in its relaxed state,

and its leaflets are attached to a rigid commissural support system. A valve that is open in its relaxed state may allow excess reflux.

Various bio-prosthetic valves have been described by prior art (see US Patents 6,562,069 and 5,500,014 as examples). However, these inventions generally describe the fixation process of chemically treating autologous or heterologous venous valve vein segments. Fixation of such biological valves usually involves gluteraldehyde, an agent that crosslinks collagen, creating a generally stiffer valve. Stiffer valves are not advantageous to have in the venous system, as they may not be sensitive enough to operate in low pressure gradients. Also, residual gluteraldehyde can cause biocompatibility issues.

CONSUMER NEEDS

Consumer Identification

The primary consumers for a prosthetic vein valve are the end users: the patient and the surgeon and interventional radiologists who implant the device. Additionally, secondary consumers are insurance companies which may include this device in its reimbursement options, as well as hospital buyers who will actually purchase the device directly for surgical use. A manufacturing plant or manufacturing team can also be considered as having certain consumer needs of a product design, since the design greatly affects the quality and cost at which manufacturing will occur. While hospital buyers and insurance companies have a financial stake in medical products, this thesis will assume that primary position of consumers belongs to those parties that most directly benefit from the design and manufacturing of the device. Thus, emphasis will be placed on the needs of patients, surgeons, and manufacturing plants.

Needs for major subsets of consumers are summarized in Table 5. It is important to understand that some of these needs are not mutually exclusive from other needs. For example, a medical device product can be made very cheaply at the hazard of reducing the quality of the product. Thus, there is an optimization process that must take place to achieve certain benefits for some consumers without imposing additional risk to other consumers. These consumer needs were described in broad terms, relevant to how each consumer would regard the prosthetic valve. From these consumer needs, quantifiable functional requirements can be determined to specify what the product must deliver.

Table 5: List of key consumers and their respective needs

	Patient Needs
1	Resolved CVI, resulting in: Decreased lower leg venous pressure Relief of pain, swelling, ulcerations Improved circulation Minimized need for post-op anticoagulation and care
2	Safe device
3	Reduced cost of surgery, but not at the hazard of reduced quality
4	Long life of device, beyond 10 years
5	Reduced hospital time without reducing necessary care for patient
6	Lower cost of operation without sacrificing options for procedures
7	Minimized need for additional surgeries
8	Reduced pain or discomfort from implanted device
	Surgeon and Interventional Radiologist Needs
1	Reduced risk of treatment using device compared to current treatments
2	Increase in patient throughput without jeopardizing necessary time in hospital
3	Wide range of device sizes to select from
4	Standardized method for selection of size
5	Sterile packaging and delivery
6	Device that is tactile
7	Diagrams and procedures for best practice of positioning, delivering, implanting
8	Ability to deliver to site accurately and safely
9	Device that can be viewed using imaging techniques (X-ray)
10	Device that is forgiving to variations in implant technique
11	Device that is designed to minimize human error
	Insurance company needs
1	Low cost to insurance companies
2	Low risk of procedure to patient
3	Demonstration of ability to support product
4	Low occurrence of second surgery or repair
	Hospital Buyer needs
1	Cost-efficient product (overall costs of operation, product, and future patient care related to CVI are reduced)
2	Demonstrated device safety and efficacy
3	Demonstrated demand for device by patients and surgeons
	Manufacturing needs
1	Traceability in components and processes – design controls
2	Ability to monitor product quality
3	High yield rates
4	Processes that are reproducible
5	Low COGS (Cost of Goods Sold)

Table 5 (continued)

6	Safe processes for operators
7	Processes are easy to learn and train for, while maintaining accuracy and reliability
8	Product that can be sterilized
9	Product that can be packaged for distribution

FUNCTIONAL REQUIREMENTS

Consumer Requirements

The critical functional requirements of a prosthetic valve were determined by translating the aforementioned consumer needs into engineering parameters that can be quantified and monitored. A Quality Functional Deployment (QFD) chart was used to make this translation, and to identify key design parameters that will affect product performance (Figure 8). The primary needs of patients, clinicians, insurance companies, hospital buyers, and manufacturing facilities were evaluated and described in three distinct categories of the QFD: 1) implantability, 2) functionality after implantation, and 3) manufacturing. These three categories were chosen because they help define broad consumer needs into more specific consumer requirements.

Valve Quality Functional Deployment	Design Parameters								Operational Parameters				Material Parameters					
Consumer Requirements	Outer diameter	Inner diameter	Length of valve	Leaflet length	Leaflet thickness	Leaflet curvature	Leaflet contact length	Orifice area	Opening pressure	Proximal static pressure	Valve leakage	Cyclic life functionality	Thrombogenicity	Surface roughness	Material composition	Material stiffness	Porosity	Suture retention strength
Implantatability																		
Implantation causes minimal localized trauma	•		•											•	•	•		
Implantation does not damage valve	•	•	•						•	•	•	•				•		
Easy to manipulate during implantation	•	•	•	•	•	•												
Can be retracted or removed if necessary	•	•	•	•	•											•		
Can be sutured easily	•	•	•													•		•
Can incorporate radiopaque tracers	•	•	•													•		
Can incorporate hooks or barbs	•	•	•													•		
Can incorporate a stent	•	•	•													•		
Functionality after implantation																		
Allows one-way flow (Patency)		•		•	•	•	•	•	•			•		•		•		
Prevents backflow of blood (Competency)				•	•	•	•	•		•	•	•		•		•		
Is functional after 500,000 open-close cycles				•	•	•	•		•	•		•	•			•		
Low thrombogenicity													•	•				
Maintains position (retention)	•		•						•			•		•		•		
Minimal leakage	•			•	•	•	•	•		•	•	•		•		•		
Causes minimal pain or discomfort	•		•													•		
Performance unaffected by vein distortion	•	•		•	•	•	•					•				•		
Minimal stress concentrations on vein wall	•	•	•													•		
Resilient to tearing					•	•	•	•		•		•					•	•
Non-toxic															•			
Non-immunogenic															•			
Non-degradable															•			
Manufacturing																		
Quality can be measured and assured	•	•	•	•	•	•	•	•	•	•	•			•		•	•	•
Fast cycle time	•	•	•	•	•	•	•	•								•		
Manufacturing processes are robust	•	•	•	•	•	•	•	•								•		
Low-cost tooling and machinery	•	•	•	•	•	•	•							•		•	•	
Can be sterilized															•			
Homogeneity within material																•	•	•
Scalable for vessel diameter	•	•	•	•	•	•	•	•								•		
Proper surface finish														•				
Design Specifications	A	B	C	D	E	F	G	H	**I**	**J**	**L**	**K**	**M**	N	O	P	Q	R
Critical Functionality Tests	-	-	-	-	-	-	-	-	**1**	**2**	**2**	**3**	**4**	-	-	-	-	-

Test	Type
1	Test for opening pressure
2	Test for reflux leakage
3	Test for cyclic life
4	Animal trial

Figure 8: Quality Functional Deployment

The “implantability” category addresses requirements that concern primarily the surgeon, as well as the patient’s well-being during surgery. Generally, a clinician wants to treat a larger number of patients in a more effective and efficient manner. This can be accomplished by having an implantation procedure that is less complex, has reduced operation time, and poses less risk to the patient than the gold standard of valve transplantation. Also a standardized method for device size selection should be developed to minimize complications that arise from incorrect selection. Thus, specific consumer requirements include that the valve is implantable with the least invasive procedure possible, that it is easy to position and manipulate during surgery, and that it can be affixed in the vein via sutures, hooks, barbs, or a stent.

The “functionality after implantation” category specifies requirements primarily for patients, but also address needs of surgeons, insurance companies, and hospital buyers. As described by Table 5, a patient receiving the prosthetic valve needs the valve to resolve their CVI, as well as be safe, economical, and have minimal risk for complications or need for additional corrective surgery. These needs can be specified into consumer requirements. For example, for a valve to resolve CVI, it needs to be patent, competent, last for a pre-described period of time, have low thrombogenecity, and maintain its position in the vein. Meeting these and other requirements in the “functionality after implantation” will improve the valve’s ability to resolve CVI, and will help improve cost, safety, and reduce risk factors leading to complications. This not only benefits the patient directly, but also the other consumers. Improved cost, efficacy,

and safety positively address the needs of surgeons, insurance companies, and hospital buyers.

Manufacturing was defined as the third main category to help specify consumer needs into consumer requirements. Any product design must be created with manufacturing in mind to reap maximum benefits in both technical and financial performance of a product. It is important to note that this category not only brings to light manufacturing needs, but also directly relates to costs that trickle down and affect patients, surgeons, insurance companies, and buyers' needs. Addressing these needs early during the design phase will help the device be better positioned to translate to a commercial and clinical setting if the opportunity arises.

Engineering Parameters

A QFD chart links consumer requirements to specific engineering parameters that can be measured and quantified. This linking of requirements to engineering parameters helps ensure that design controls can be placed on the parameters to achieve and surpass key consumer requirements. Three main types of engineering parameters were identified: 1) design parameters, 2) operational parameters, and 3) material parameters. Design parameters were inclusive of geometric information that defined the physical shape and size of the device. Operational parameters included performance attributes of the valve that could be assessed with testing; these operational parameters that became the bulk of this research. Material parameters involved quantifiable aspects of the valve material. While these parameters are very important to the design of any medical device, for this

particular device they are governed primarily by the initial material selection. Accordingly, after the initial material selection, less emphasis was placed on the material parameters, and more emphasis was placed in addressing the design and operational needs

Linking Requirements to Parameters

After consumer requirements were specified and engineering parameters were identified, each parameter was examined to assess which requirements it addressed in the QFD, and the link was denoted with a dot mark. In a commercial product development cycle, many tests are used to evaluate and verify a product's engineering parameters. However, due to time and resource limitation, this research concentrated on evaluating the valve's functionality based on the most critical engineering parameters. The primary objective of this research was to create a prosthetic vein valve that demonstrates functionality for eventual clinical use. Thus, emphasis was placed on evaluating operational parameters, simply for the fact that these parameters were directly related to the functionality of the device after implantation. Design features such as leaflet thickness, curvature, and contact length also play a role in the functionality of the device. However, rather than creating tests that evaluate geometric features, tests were created to evaluate operational parameters. This created a more clinically relevant evaluation of device functionality.

Critical Engineering Parameters

Five parameters (four operational parameters and one material parameter) were designated as critical in producing a functional vein valve. From an operational standpoint, opening pressure, proximal static pressure, cyclic life functionality, and valve leakage were all parameters that could be measured to quantify product performance. These parameters, above all other engineering parameters, defined the valve's functionality in the most critical manner. These are testable parameters with *in vitro* bench studies, and test results will characterize the valve's functional performance.

The most critical material parameter for designing a prosthetic vein valve is thrombogenecity. Thrombogenecity of a material is its property of eliciting thrombus formation on its surface. Thrombus formation, as described previously, is a major cause of prosthetic valve failure and often leads to obstruction. With almost all medical devices, low thrombogenecity is a material parameter that is desired. Thrombogencity can be measured by performing histological analysis of a surface area after the material has been exposed to blood with *in vivo* animal testing. While this thesis identifies thrombogenecity as a critical engineering parameter, it is beyond the scope of the thesis to create a test for it. However, a pre-clinical animal trial has been planned, and will be conducted within the coming months to assess the thrombogenecity and patency of the device.

DESIGN SPECIFICATIONS

Three critical design specifications were imposed on the valve, including that the device 1) withstand 300 mmHg of backpressure with less than 1.0 mL/min of leakage, 2) open with distal pressure gradients less than 5 mmHg, and 3) withstand 500,000 cycles of opening and closing while meeting or exceeding design criteria 1 and 2. These critical design specifications stem from design specifications I, J, K, and L from Table 6 below. Table 6 depicts design specifications for each of the engineering parameters that were identified in the QFD chart (Figure 8). The reasoning used for developing these specifications can be found in the section titled "Justification of Design Specifications," immediately after Table 6.

Table 6: Engineering parameters and relevant design specifications

Item	Design Parameter	Design Specification
A	Outer diameter	The largest outer diameter (OD) should not be greater than 1.2 times the diameter of the vein.
B	Inner diameter	The area of the valve's lumen should not be less than 90% of the area of the vein's lumen.
C	Length of valve	A length between 1.5 and 2.5 times the OD of the valve is desirable.
D	Leaflet length	The leaflet length should range between 1 and 2 times the diameter of the vein.
E	Leaflet thickness	Each leaflet thickness should be less than 5% of the valve diameter.
F	Leaflet curvature	The leaflet curvature could range between being flat panels to have a radius equivalent to half of the valve diameter.
G	Leaflet contact length	Sealing contact length should range between 20 and 50 percent of the diameter of the valve.
H	Orifice area	The open position the orifice area should be greater than 30% percent of the cross-sectional area of the vein.

Table 6 (continued)

Item	Operational Parameter	Design Specification
I	Opening pressure	The pressure gradient required to open the valve and cause forward fluid flow must be less than 5 mmHg.
J	Proximal static pressure	Valve must structurally bear at least 300 mmHg of static pressure and must comply with valve leakage specifications
K	Valve leakage	The valve must not leak more than 1.0 mL of fluid per minute at any proximal pressure level maintained for a period of 30 seconds.
L	Cyclic life functionality	The valve must open and close in simulated physiologic conditions at least 500,000 cycles, and meet design specifications I, J, and K.
Item	**Material Parameter**	**Design Specification**
M	Thrombogenicity	The valve and material must not promote significant thrombus formation over a period of three months in an animal trial.
N	Surface roughness	No current specification.
O	Material composition	The valve must not bio-degrade when implanted in the human body.
P	Material stiffness	Material stiffness less than 1 GPa is desirable.
Q	Porosity	Material porosity uncommon to polymeric chemical structure, such as holes, bubbles, or voids, must not be present.
R	Suture retention strength	A single 6-0 prolene suture should have a pull-out strength of at least 2.4 Newtons when subjected to AAMI VP20 -1994 Section 5.8 protocol.

Justification of Design Specifications

A. **Outer diameter** - For the scope of this thesis, the valves were designed for implantation into a human adult Common Femoral Vein (CFV), which has an average diameter of about 12 mm [38]. For purposes of testing valves using standard tubing and fittings, it was more practical to design valves for a 10 mm inner diameter vein, and thus prosthetic valves were sized according.

B. **Inner diameter** – The lumen of the valve be as large as possible for decreased flow resistance. However, another important requirement is that the thickness of the valve is sufficient for implantation and fixation. A reasonable compromise between the two requirements is that the area of the valve's lumen should not be less than 90% of the area of the vein's lumen.

C. **Length of valve** – A length between 1.5 and 2.5 times the OD of the valve is desirable. The length should be short enough that the valve does not interfere with the hemodynamics of branch flow near the valve site, yet long enough to provide longitudinal stability.

D. **Leaflet length** – In a natural bi-leaflet vein valve, the leaflet length is usually twice the diameter of the vein [39]. A prosthetic vein valve's leaflets can probably be shorter and still function. The leaflet length should range between 1 and 2 times the diameter of the vein.

E. **Leaflet thickness** – Natural vein valves have leaflet thicknesses ranging between 20 and 50 microns, and derive their strength from collagen in the leaflet [14]. The leaflets of a prosthetic valve can be made that thin; however the strength of the leaflets may not suffice for valve functionality. Generally, the leaflets should be made as thin as possible without sacrificing competency and cyclic life functionally. As a reasonable specification, the each leaflet thickness should be less than 5% of the valve diameter.

F. **Leaflet curvature** – Natural vein valves have a parabolic shape, enabling antegrade flow at low opening pressures and competency at high proximal pressure. A prosthetic vein valve could mimic this anatomy to enhance its

functionality. The leaflet curvature could range between being flat panels to have a radius equivalent to half of the valve diameter.

G. **Sealing contact length** –The sealing contact length is the axial distance that the leaflets coapt to form a sealing surface. This length should be sufficient to prevent leakage; *in situ* cusp contact length is generally 1/5 to ½ the inner diameter of the vein [40]. This indicates that a prosthetic bi-leaflet valve's sealing contact length should range between 2 and 5 mm for a prosthetic having a 10 mm OD.

H. **Orifice area** – B-flow ultrasound scanning techniques by Lurie et al revealed that the cross-sectional orifice of an open valve is about 35% of the area of the vein cross-section distal to the valve [15]. Thus, a prosthetic valve should have similar or better orifice area, and therefore should be greater than 30% of the normal vein cross-sectional area. Also, it is important to note that a natural valve's orifice is elliptical in nature. The major axis of the ellipse is the inner diameter of the vein and the minor axis is the distance between the two cusps.

I. **Opening pressure** – Human vein valves are typically open when a human is at rest in the standing or sitting position. Blood flow during these situations is driven not by the calf pump, but by *vis a tergo* flow from the suction of the right atrium of the heart. The pressure gradient driving this venous flow is quite low, and native vein valves typically open with less than a 5 mmHg pressure gradient. Thus, a prosthetic vein valve must be designed to open with the same pressure gradients.

J. **Proximal static pressure** – Normal physiologic static pressure imposed proximally on the valves of the CFV range between 35 mmHg to about 50 mmHg. This is the result of the hydrostatic pressure column of blood from the right atrium of the heart to the most proximal valve [16, 17]. During the valsalva maneuver, pressure in the veins of the upper leg can increase to nearly 100 mmHg [41]. The valsalva maneuver occurs when the glottis is closed. This includes actions in everyday activity, such as lifting a heavy object, having a bowel movement, or exercising. Venous static pressure near the foot is normally between 90 and 100 mmHg [42]. While this prosthetic valve was initially designed for implantation into the common femoral vein, it is certainly scalable for other vein sizes and locations. Also, there may be a real need to implant several valves spaced throughout the leg veins to combat the more severe cases of CVI, and thus a prosthetic valve should withstand the venous environment of the lower leg veins as well. Thus, while 100 mmHg is the average maximum static venous pressure, it can be estimated in worst-case scenarios that maximum venous pressure could be 150 mmHg. Applying a safety factor of 2 then results in design specification J: the valve must functionally and structurally withstand 300 mmHg of proximal pressure.

K. **Valve leakage** – Valve leakage can only occur when there is a positive pressure gradient applied from the proximal side of the valve. During rest in either a standing or sitting position, the prosthetic vein valve will be open, and the valve will not leak in the retrograde direction during this time. However, reflux could occur during a sudden change in posture from sitting to standing, or during

muscle movements such as calf pumping. The calf pumps approximately 10 to 20 mL of blood through the deep leg veins with each muscle constriction [9]. It is reasonable to consider a valve functional even if it allows leakage less than 10% of blood volume flowing in the antegrade direction per calf pump. Of the lower limit of 10 mL per stroke, 10% imposes a leakage condition of 1.0 mL of blood. It is important to normalize this per time; a metric that can be used to assess the competency of a vein valve is its leak-rate (volume of leakage per minute).

L. **Cyclic life functionality** – Any implanted medical device must have reasonable longevity and remain functional throughout its intended life. There are certain "rules of thumb" that medical device companies use for specifying intended life of their products. For artificial heart valves, companies design their products to withstand "10 years, 40 million cycles" as a target life expectation, based on the number of heart beats in the average human. Prosthetic vein valve life can also be assessed in a similar manner. The dynamics of the valve opening and closing during calf pumping action cause the most relevant forces on and displacement of the valve structure. These forces and displacements cyclically fatigue the valve, especially the leaflets. The calf pumps about 40 times a minute (0.67 Hz) during normal walking cadence [8, 9]. This research assumes that an elderly patient would have such a brisk walking cadence, and is actively walking a total of about 1 hour a day. This means that in an average day, the valves will open and close about 2400 times. In one year, the valve will open about 876,000 times. Thus, if the valve is to last 10 years, it should be able to cycle nearly 9 million times and still remain functional. Cyclic performance depends on two main factors: good

design, and good manufacturing. It is a reality that a valve fabricated in a lab environment without statistically controlled manufacturing processes will not meet this design criterion. Such performance demands precision manufacturing that expensive machinery, tooling, and quality control can provide. However, if a lab-fabricated valve can achieve even 5% of this cyclic life criterion, it will have demonstrated concept feasibility of the design. Thus, the design criterion for a lab-fabricated valve is to remain functional after 500,000 cycles of opening and closing.

M. **Thrombogenicity** - Thrombus formation should be kept to an absolute minimum. The best method for evaluating thrombus formation is to implant the valve into the venous system of an appropriate animal model. Animal models that could be appropriate include canine, porcine, and ovine models. Histological analysis using Carstairs stain can quantify thrombus formation. The valve should elicit thrombus formation that is less than or equivalent to the amount caused by current vascular graft products containing Dacron® or ePTFE.

N. **Surface roughness** – In general, the lower the surface roughness, the less impact the surface will have on thrombogenesis.

O. **Chemical composition:** No specification or limitation. It is, however, strongly recommended that materials known to have chemical compositions that are stable, biocompatible, non-toxic, and non-immunogenic be used for the device. It is highly recommended that the material used for a vein valve is a material that has been used in FDA-cleared medical devices.

P. **Material stiffness** – There is no defined elastic modulus that the valve material should have. However, one guideline to use suggests that the material stiffness should be similar to that of native vein and vein valves, or less than 1 GPa. Also, the prosthetic valve material should have a breaking strength equivalent to or greater than native valves, which is between 8 and 10 MPa [43]. Material stiffness is a very important parameter because it impacts the severity of stress concentrations that are imposed on the vein wall. Low material stiffness will impose less stress concentrations and less trauma by radial force than high material stiffness.

Q. **Porosity** – No current specification. Porosity specifications can vary depending on the material the valve is comprised of, and what the constituents are in the event composites are used. For example, if Dacron ® is incorporated into the valve, porosity will be present due to the inherent nature of the mesh. Porosity may be advantageous in some situations, because it promotes neointimal growth and could facilitate circumferential sealing of a valve having a central orifice. However, unwanted porosity can reduce cyclic life significantly, and will adversely affect the valve's structurally integrity. Thus, as a general guideline, material porosity uncommon to specific polymeric chemical structures, such as holes, bubbles, or voids, must not be present.

R. **Suture retention:** The Association for the Advancement of Medical Instrumentation (AAMI) has developed a protocol for suture retention in vascular grafts, outlined in AAMI VP20-1994, Section 5.8. A conservative engineering analysis was used also to determine the desired suture retention strength.

Equations 1 and 2 were used to calculate the desired suture retention strength. Table 7 describes the parameters used in the calculation.

Table 7: Description of variables and values used to calculate suture retention strength

Variable	Description	Value
F_{suture}	Suture retention strength	Unknown
$F_{max,proximal}$	Maximum proximal force imposed on valve	Unknown
$P_{proximal}$	Maximum proximal pressure	40,000 Pascals (300 mmHg)
$A_{cross\text{-}section}$	Cross-sectional area of 10 mm diameter valve	0.0000785 m^2
SF	Desired safety factor	3
n	Number of interrupted sutures desired on a 10 mm valve proximal end	4

Equation 1: Desired suture retention strength

$$F_{suture} = \frac{SF \cdot F_{\max, proximal}}{n}$$

Equation 2: Maximum proximally applied net force on valve in femoral vein

$$F_{\max, proximal} = P_{proximal} A_{cross-section}$$

Thus, the desired suture retention strength of the valve using 6-0 Prolene sutures is 2.4 N. For future development of the valve, this can be tested using the AAMI VP20-1994 protocol for Cardiovascular Implants – Vascular Prosthesis. For comparison, the AAMI protocol for 6-0 Prolene suture material showed suture retention strength for porcine carotid arteries to be 7.2 ± 3.1 N [44]. In 1999, Niklason reported a tissue-engineered vascular graft having a suture retention

strength of 0.9 N [45]. Thus, a design specification of 2.4 N as the suture retention strength is of the same order to biologic vessels and prosthetic vascular grafts, and is a reasonable specification.

Final Relevant Design Specifications for Functional Testing

Table 8 lists the final clinically relevant design specifications for the scope of this thesis. These final specifications stem largely from the operational specifications, and were defined in terms of three important clinical parameters: patency, competency, and cyclic life functionality. Low thrombogenecity is another key design specification that a clinically functional valve must meet. However, it is beyond the scope of this thesis to test for thrombogenecity. Thus, all subsequent tests and results are based on demonstrating valve functionality for the first three key clinical parameters. Also, while the remaining design specifications in Table 6 are all important, the final design specifications were chosen because functionality can be easily traced and assessed for these specifications.

Table 8: Critical Design Specifications for testing valves

Specification Number	Parameter	Design Specification
1	Patency	The pressure gradient required to open the valve and cause forward fluid flow must be less than 5 mmHg.
2	Competency	Valve must structurally bear at least 300 mmHg of static pressure and must not leak more than 1.0 mL/minute for all tested pressure from 0 to 300 mmHg.
3	Cyclic life functionality	The valve must open and close in simulated physiologic conditions for at least 500,000 cycles, and continue to meet design specifications 1 and 2 at all test intervals.

Table 8 (continued)

Specification Number	Parameter	Design Specification
4	Low thrombogencity	The valve must elicit less thrombogenesis in a three month span in an animal trial than common vascular graft materials such as Dacron® and ePTFE. Tests **will not** be conducted for this design specification as it is beyond the scope of this thesis.

Indications

The device and all configurations are to be used only to treat CVI patients who have symptoms of severe pain, leg swelling, and ulcerations, and confirmed primary or secondary venous valvular incompetence. This device is indicated for use in leg veins, and should be implanted at a site distal to the iliac vein, below the inguinal canal. The device is for use in veins having diameter greater than 3 mm. The device should be implanted in a location where the vein wall is structurally intact. Only a clinician trained in treating CVI should prescribe this product.

Contraindications

This device is not indicated for use in patients exhibiting phlebitis, infection, or cancer in the legs. The device should not be used in patients who have existing cardiac pathologies that limit cardiac output. The device is not indicated for use in patients who may be at adverse risk during implantation surgery. The device should not be implanted into veins having diameters less than 3 mm. The device should not be implanted at the same site a damaged native valve exists; the damaged native valve should be removed in a valvulotomy.

CHAPTER 2

METHODOLOGY

MATERIAL SELECTION

While there are various materials that are researched for biomedical use, there is quite a limited selection of materials that are presently used in medical devices cleared by the FDA (Food and Drug Administration). The primary objective of this research was to create a functional prosthetic vein valve for eventual clinical use. This implies that if the technology is to reach patients, it must be commercializable and also achieve FDA clearance. Thus, material selection was based on existing materials that have been used in medical devices sold in the U. S. It is important to note that the FDA does not clear or approve specific materials for clinical use; it only clears devices. However, it is a good starting point to consider the materials used in FDA-cleared medical devices as potential candidates for use in a prosthetic vein valve.

Commonly used materials in cardiovascular medical devices include polytetrafluoroethylene (PTFE), expanded- polytetrafluoroethylene (ePTFE), polyethylene teraphthalate (PET), and polyurethanes (PU). Other materials include polyesters, hydrogels, silastics, collagens, elastins, Room Temperature Vulcanized (RTV) rubbers, and silicone.

There are several critical design specifications that a material must meet or exceed to be considered for use in a prosthetic vein valve, described in detail earlier in Table 6. The

material must have low thrombogenecity, low surface reactivity, low surface roughness, must elicit low immunogenic response, and must maintain chemical and compositional stability during the intended functional life. Additionally, the material cost should be low, and should be easy to manipulate into various shapes for the valve design. Ideally, the valve should be flexible, and thus the material should have mechanical properties that are conducive to valve flexibility. Also, the material must be able to incorporate sutures, stents, or other thin metal hooks or barbs without tearing or degrading. Available materials were assessed based on these requirements.

A material called poly(vinyl-alcohol) cryogel (U.S. Patent 5,981,826), was used throughout this research as the material of choice [46]. Poly(vinyl alcohol) (PVA) cryogel is a material within the class of hydrogels. Hydrogels have the unique property of being hydrophilic, meaning they are compatible with an aqueous environment such as the human body. Hydrogels can be created to have a wide range of stiffness and are easy to mold and shape. A hydrogel generally needs to have its chemical and physical composition stabilized via cross-linking. Cross-linking can be achieved by chemical fixation, however this process often renders the hydrogel less biocompatible. Another method of cross-linking is via a sequence of freezing and thawing the hydrogel. With each successive freeze-thaw cycle, a hydrogel increases its bulk stiffness. This method prevents non-biocompatible chemicals from entering the hydrogel.

PVA has been shown to have very low thrombogenecity [47, 48]. Additionally, it is biocompatible and is being used in FDA-cleared medical devices. PVA is easy to

manufacture, and can be poured or injected into molds for creating a product. It can be made to be highly elastic or extremely stiff by varying the material composition or processing techniques. Cross-linking PVA with freeze-thaw cycles, and thereby creating the cryogel, affords the material greater biocompatibility than chemical fixation.

PTFE and ePTFE materials, such as Gore-Tex ®, are relatively stiffer materials, and while useful for vascular grafts, may be too stiff for use in a vein valve, an application where a more elastic material would be advantageous. Generally PTFE and ePTFE should be created in the shape of the desired medical device; vascular grafts are often manufacturing using an extrusion process. Valve geometry is more complex than tubular geometry, and manufacturing a valve of PTFE and ePTFE could be an expensive process.

PET materials, such as Dacron® (DuPont), are used often as a vascular graft material. These grafts use woven PET fibers to create a porous mesh that promotes intimal growth of the surrounding vasculature, as well as some thrombus formation. While this material and composition work well for a graft, it will be complicated to fabricate into the shape of a valve. Also, PET elicits thrombus formation, something that should be minimized in a venous environment.

Various rubbers, silastics, and silicone materials are advantageous for valve material because of their elasticity. Different chemical compositions and manufacturing processes can vary the stiffness of these materials, and thus the flexibility of the valve can be

adjusted as needed. However, these materials also tend to be brittle in nature, a characteristic that is a disadvantage for a valve.

Biologic materials such as collagens and elastins as well as small intestinal submucosa (SIS), are good materials for creating a valve that has similar mechanical properties to a natural valve. Natural valve leaflets are comprised of collagen fibers, and the valve derives much of its strength from the arrangement of these fibers. However, collagen and elastin must be obtained from a biologic source: either a human donor or an animal donor. SIS is typically derived from pigs. Tissue, collagen, and elastin can be chemically treated or cryopreserved to fix the mechanical properties and prevent degradation. It is generally known that gluteraldehyde, while an effective fixation agent, can cause carcinogenic and immunogenic responses from tissue surrounding the implanted device. Also, gluteraldyahyde tends to increase the stiffness of the tissue it is fixing, which could increase the pressure gradient required to open the valve. Additionally, studies have shown that cryopreserved vein valves elicit an immunogenic response, and the structural integrity of the valves was affected by the freezing and thawing process [32]. Tissue, collagen, and elastin processing is complex; quality control of such a prosthetic valve is not an easy matter, when compared to a valve involving more traditional manufacturing techniques. Thus, because of complications that can arise from chemical fixation and cryopreservation, bioprosthetic valve designs were not considered for this research.

CONCEPT DEVELOPMENT

Concept 1: Bileaflet Valve – Pre-open commissure

The first concept design for a prosthetic vein valve involved a bileaflet valve with its leaflets positioned slightly open. Pre-opened leaflets afford the advantage of ensuring valve patency. This can be beneficial in the leg veins during rest, where the pressure gradient driving blood flow back to the heart is typically less than 5 mmHg. However, during reflux, the open leaflet configuration must still close sufficiently to achieve competency and maintain leakage below 1.0 mL/min.

This valve prototype, along with prototypes for Concept 2 and 3, was created by injecting PVA into a silicone two-part mold. A complete description of how silicone molds were made can be found in the section titled "Valve fabrication." The valve dies for making the molds were created by hand using clay, and carefully sculpted into their final shape with needle-point forceps and surgical scissors. The clay was baked at 130 °C for about 30 minutes. The hardened clay valve dies were finished and polished with jeweler's files. This positive die was then used to create a two-part silicone cavity mold for creating valves of PVA. The same methodology for creating two-part silicone molds was used for all concepts employing injection molding of PVA.

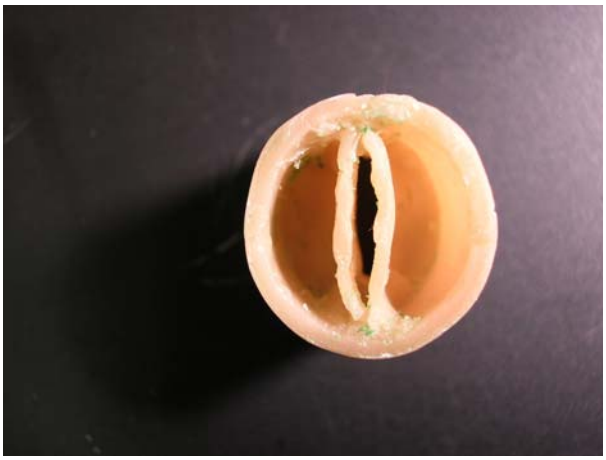


Figure 9: Design concept 1 – bi-leaflet valve with pre-opened leaflets (proximal view)

The distinguishing feature of this valve design is that the leaflets are positioned to create a slightly pre-opened commissure. This design was created with the hypothesis that a pre-opened commissure would facilitate patency, while physiologic proximal pressure would be sufficient to cause the leaflets to coapt and seal. Each leaflet arcs towards the lumen of the valve, meeting at the middle. During reflux, the valve's leaflets should deform under proximal pressure and touch to create a sealing plane. This plane is a critical feature of the prosthetic valve; a plane of contact provides more sealing surface than just a line of contact sealing. In a tortuous and dynamic venous environment, leaflets creating line contact may not seal as effectively as leaflets creating planar contact.

Concept 1 testing:

A prosthetic valve of Design Concept 1 was created by injecting 15% PVA into a two-part silicone mold. The valve underwent 3 freeze-thaw cycles, with a freezing time of 12 hours and a thawing time of approximately 3 hours.

The valve was placed in a clear plastic tube having a 10 mm inner diameter. The valve was then exposed to a 100 cm column of water, thus imposing a pressure of 100 cmH20 (approximately 74 mmHg) on the valve leaflets. However, it became immediately clear that this valve design did not seal against reflux. The pre-opened leaflets simply did not coapt like they were intended to. The leak-rate was approximately 1 mL per second, much higher than the design criteria of 1 mL per minute. Based on this failure of competency, the idea of a valve manufacture of PVA with pre-opened leaflets was discounted. A flexible valve having leaflets that are not pre-opened could seal more effectively against reflux.

Concept 2: Bileaflet Valve – Pre-closed Commissure

The structure of this valve is essentially the same as Design Concept 1. However, in this case, the leaflets are not pre-opened, but rather are sealing in their natural state. When the valve is free from any externally applied forces, the leaflets contact each other without exerting force on each other. This absence of a spring bias in the leaflets ensures that resistance to antegrade flow is minimized, a desirable attribute of a valve design. A valve closed in its relaxed state may prevent leakage of blood during retrograde flow better than a valve that is open in its relaxed state. This valve prototype was also created by using clay to make a two-part silicone mold (Figure 10), and then injecting PVA into the cavity mold (Figure 11).

Figure 10: Design concept 2. Clay positive dies (left) are used to make two-part silicone molds (right)

Figure 11: Design concept 2. PVA valves are made in silicone mold via injection molding (left). One PVA valve is removed and compared to clay die (right). The PVA valve had dried for about 30 minutes; hence it shrank slightly in size.

Concept 2: Initial testing

A 10 mm diameter valve was placed in a 10 mm ID flexible tube composed of Salubria® biomaterial (Salumedica, LLC, Atlanta GA) for initial evaluation of leakage during reflux. The valve was placed such that a plastic fitting abutted to the distal end of the valve to prevent valve migration. The tube with valve was tied onto another plastic fitting connected to a hand-operated syringe pump, with a pressure transducer measuring

proximal hydrostatic pressure. At a pressure above 20 mmHg, leakage occurred profusely around the circumference of the valve. Because this did not appropriately evaluate the valve, testing was stopped, and a redesign of the valve was initiated.

Concept 2: Redesigned with flared edges for sealing

A flared inlet and outlet were added to the bileaflet valve to help seal against circumferential leakage. The concept of a flared inlet or outlet is multi-purposeful. It facilitates circumferential sealing of the valve against the intimal layer of the vein wall. Circumferential sealing is paramount in preventing leakage during retrograde flow, and the flared inlet and outlet ensure that a good seal is created. The flared inlet and outlet may help alleviate stress concentrations in the vein wall during distension. In essence, the inlet and outlet were designed to help smoothly transition the vein wall from a diameter equivalent to the vein valve to the vein's distended diameter, minimizing damage to the vessel wall. This will be particularly helpful if the remaining sinus region of the affected vein is intact, and needs to distend in its natural manner.

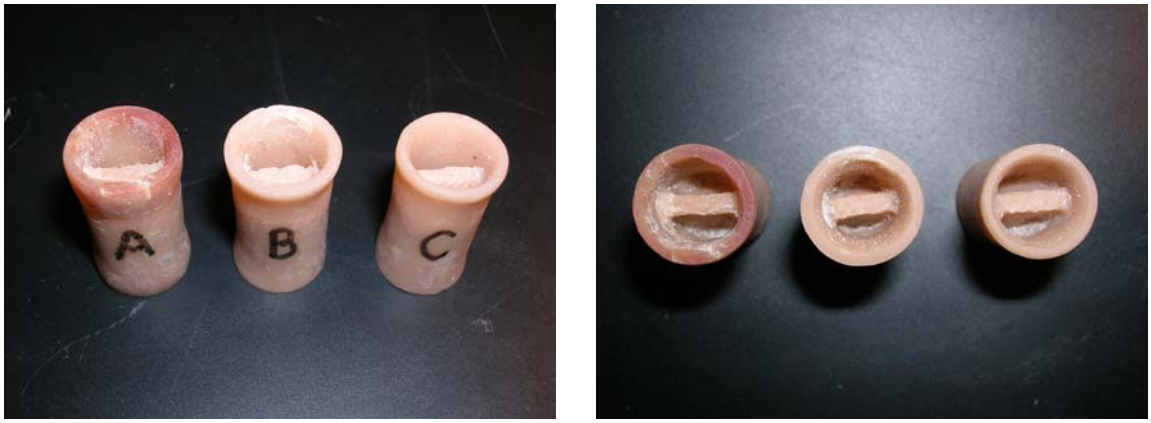


Figure 12: Clay valves for positive die for fabricating re-designed concept 2.

Figure 13: Clay valves for positive die for fabricating re-designed concept 2. Note the slight flaring of the valves at the ends to facilitated circumferential sealing.

Figure 14: Positive dies and negative two-part silicone molds formed around the clay dies. The mold bottom is on the left, the mold top is on the right.

Redesigned concept 2 testing:

The redesigned bi-leaflet valve demonstrated competency at physiologic proximal pressures (35 to 50 mmHg), and opened at a pressure of 5.9 ± 0.9 mmHg when placed in the Salubria® tube. Figure 15 depicts the valve's leak-rate performance for proximal pressures ranging from 0 mmHg to over 300 mmHg. At pressures below 230 mmHg, the valve met the design criteria of having a leak-rate less than 1.0 mL/min. The valve's

opening pressure did not meet the opening pressure design criteria of less than 5 mmHg. However, the opening pressure is reasonably close, and demonstrates the concept's potential to meet the design requirements. With minor improvements in design, material, and manufacturing, this valve concept was deemed to have potential for functionality even at 300 mmHg.

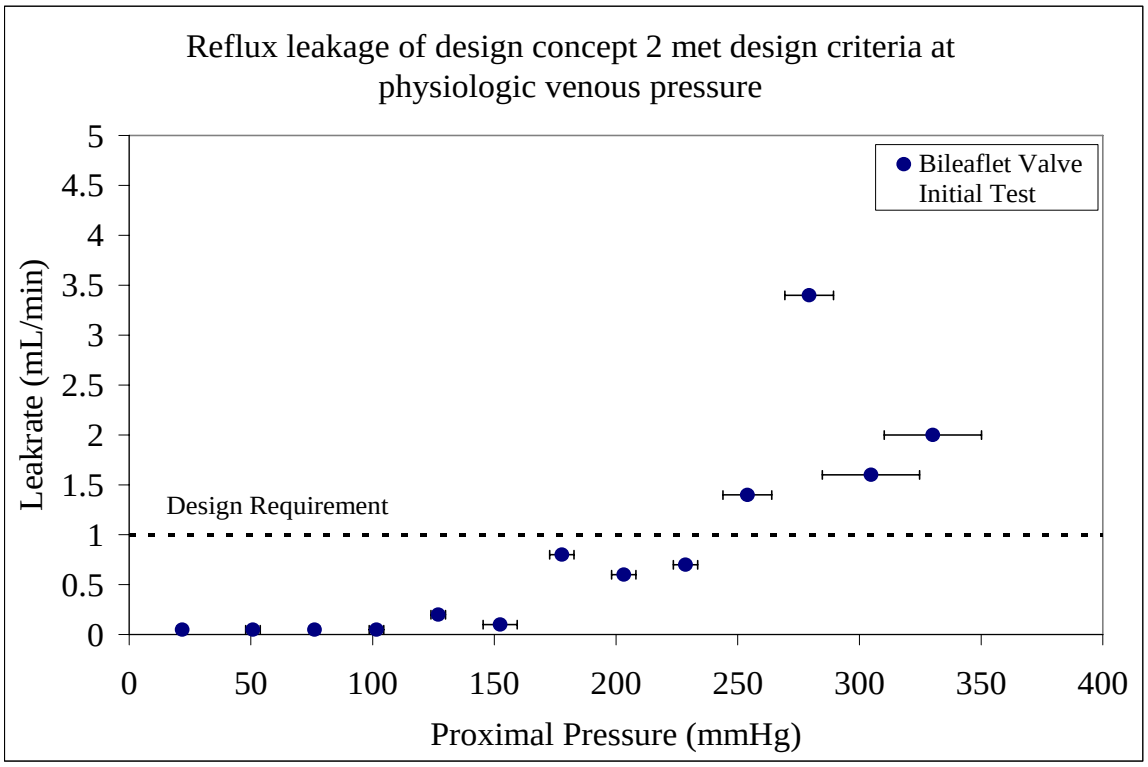


Figure 15: Design Concept 2 meets proximal pressure criteria at physiologic venous pressures, and shows promise to be functional at higher pressures

Design Concept 3: Parabolic valve

This valve design is unique in that it allows forward flow around the circumference of the valve, rather than through a central orifice as most conventional valves do. The design intent of this concept was to help negate concerns of circumferential leakage. Thus,

rather than trying to prevent circumferential leakage, the valve utilizes the circumference as the flow path during antegrade flow, with the periphery of the paraboloid seal against the vein wall during reflux.

Figure 16: Parabolic valve designs. Isometric view (left) and top view (right)

Figure 17: Parabolic valve side view (left) and bottom view (right)

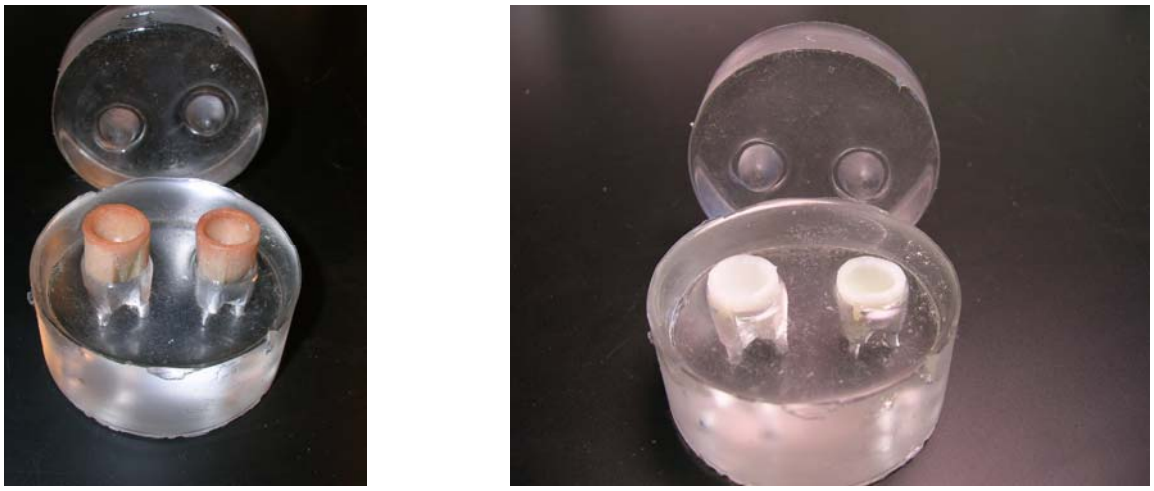


Figure 18: Parabolic valve dies being extracted from mold (left). PVA valve being extracted from mold (right)

Figure 19: Side view (left) and distal view (right) of parabolic valve clay dies compared to PVA valves. The valves had dried for 30 minutes, hence the slight shrinking in size.

The valve was designed to be anchored to the vein via three fins that extend distally from the paraboloid. Anchoring could be achieved by suturing the fins into place, with transmural interrupted sutures. Another mode of fixation could incorporate a balloon-expandable or self-expanding stent into the distal half of the valve. For purposes of concept testing, anchoring was not pursued. Instead, fixation was achieved using retention rings.

Concept 3 testing:

The parabolic valve allowed a leak-rate greater than 1.0 mL/min at proximal pressures greater than 50 mmHg (Figure 20). The opening pressure for the parabolic valve was 26.4 ± 4.6 mmHg, far greater than the design criteria of 5 mmHg. The fins were prone to failure; one of the fins cracked and buckled at a pressure of about 150 mmHg.

Based on the poor performance of this concept, a parabolic, circumferential flow valve was not considered a very good option for a prosthetic vein valve.

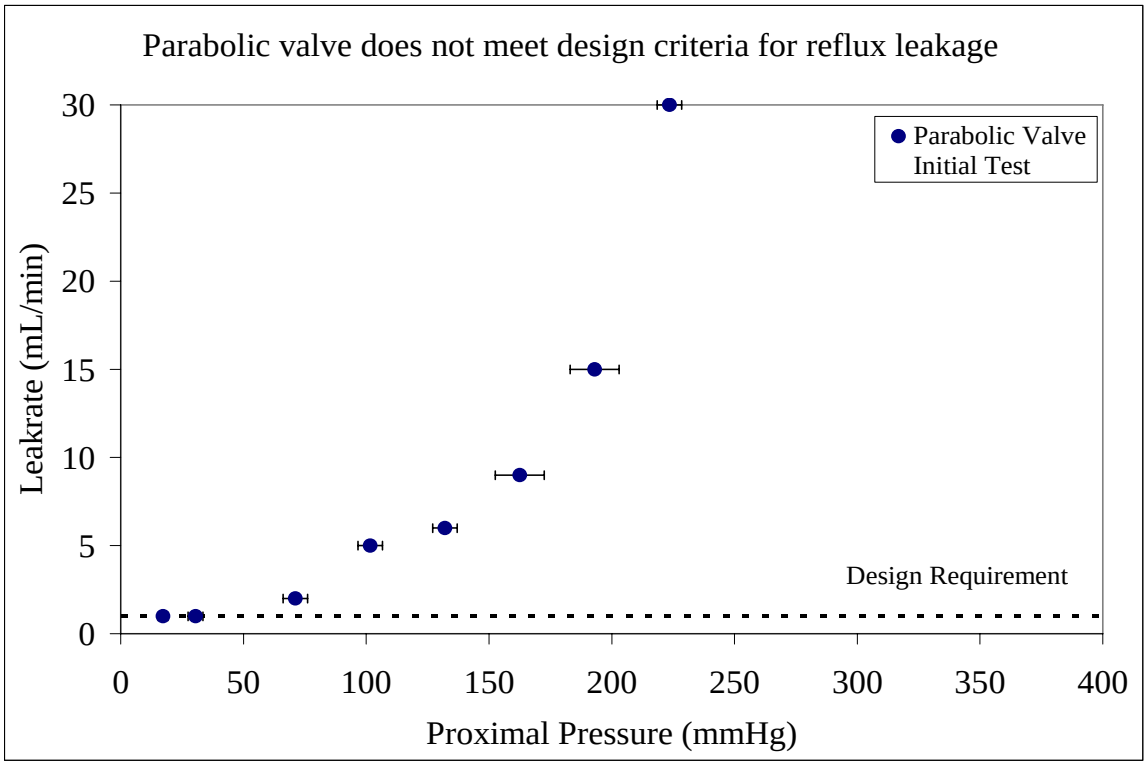


Figure 20: Parabolic valve leaked excessively and did not meet design criteria for reflux leakage

Design Concept 4: Ball and Cage Valve

Ball and cage valve designs have traditionally been used as cardiac valve replacements (Figure 21). It is reasonable to at least consider existing cardiovascular medical devices for use as a prosthetic vein valve. However, there are several disadvantages that prevent a ball and cage valve from being a contending design as a vein valve. First, veins are thin, flexible, collapsible tubes, and placing a bulky, rigid object like a ball and cage valve can erode through the vein walls. Secondly, ball and cage valve operation is driven primarily by bulk fluid flow, not fluid pressure. This valve type requires high blood flow conditions to move the ball and open the valve. There is neither high velocity nor high blood flow conditions in the venous system of legs, and implanting a ball and cage valve in that environment would be a poor decision.

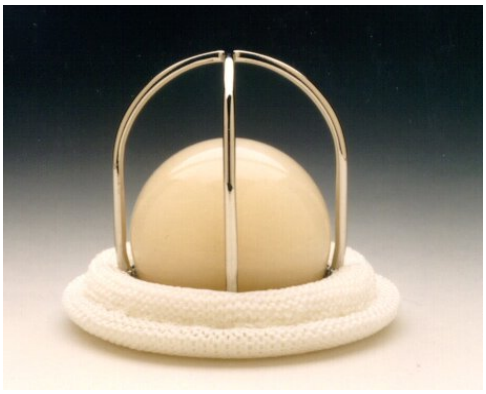


Figure 21: Starr-Edwards ball and cage models (Baxter International, Inc.)

Figure 22: Clay model of a ball-and-cage vein valve. No further work was pursued with this model.

Design Concept 5: Mechanical Leaflet Valve

Mechanical leaflet heart valves can be considered as an option for venous valve replacement, albeit they are probably the last option for the venous environment. Failure of prior attempts at using mechanical heart valves is evidence enough that a metal valve will cause multiple problems of trauma, inflammation, thrombosis, and intimal growth [30]. While mechanical valves are suitable as heart valve replacements, the flow and pressure conditions of the heart vastly differ from leg veins, and more suitable vein valve prosthetic designs should be examined. Thus, mechanical leaflet valves were not considered as a feasible option for this research.

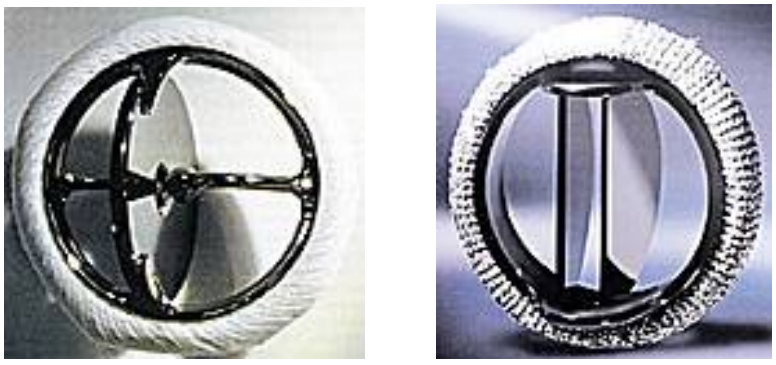


Figure 23: Tilt-disc and bi-leaflet mechanical heart valves (St. Jude Medical, Inc)

Design Concepts and Implantation Modes

Throughout this research, emphasis was placed on creating a functioning valve that could be tested *in vitro*. *In vivo* work, particularly implantation technique, is a vital part of any product development phase for a medical device. However, implantation using standard stenting and catherization necessitates incorporation of commercially available vascular interventional products. Until recently, the valve in this research had not reached development maturity for the incorporation of commercial products to be a practical prospect. It was impractical to test the valve's implantability during the scope of this research; testing the valve's functional performance was a greater priority. Thus, this research does not include any test results or concentrated design efforts on catheterization, stenting, or the use of hooked or barbed protrusions. Nevertheless, valve concepts were designed to be conducive to various implantation techniques. The discussion section (Chapter 4) will discuss potential implantation techniques.

Design Selection Process

Five critical engineering parameters were selected as the metrics for analyzing Concepts 1, 2, and 3 for potential functional performance. Concepts 4 and 5 were abandoned since historical data did not support their use. A Pugh Chart (Table 9) was used to summarize each design's performance or potential for performance in relation to the most critical engineering parameters. A plus sign (+1) denotes a case where a design has either demonstrated functionality or shown potential to demonstrate functionality with respect to an engineering parameter. A minus sign (-1) denotes a case where the design failed to

be functional or failed to show promise of functionality. A zero (0) denotes a case where the design's performance is unknown based on lack of testing.

Table 9: Pugh Chart used for design selection

	Design Concept		
Critical Parameter	**Bileaflet Valve: Open Orifice**	**Bileaflet Valve: Closed Orifice**	**Parabolic Valve**
Opening pressure (less than 5 mmHg)	+1	+1	-1
Proximal static pressure (up to 300 mmHg while incurring no more than 1.0 mL/minute leak-rate)	-1	+1	-1
Cyclic life functionality (maintain opening pressure, proximal static pressure, and valve leakage requirements even after 500,000 cycles	0	0	-1
Thrombogenecity (Significant thrombus formation is not desired)	+1	+1	+1
Total Score	**1**	**3**	**-2**

Summary of concept testing and description of scoring

A bi-leaflet valve with a pre-opened orifice allowed forward flow with less than a 5 mmHg pressure gradient. Concept testing showed that the bi-leaflet valve with a sealed orifice has promise of opening with a pressure gradient less than 5 mmHg. Thus both concepts were assigned a +1 for the opening pressure parameter. However, the parabolic valve needed an opening pressure above 20 mmHg, well above the design criteria, and thus the valve was assigned a -1 value for that parameter.

Of the three designs, concept testing showed that the bi-leaflet valve with closed leaflets was the only valve that demonstrated potential of withstanding 300 mmHg of backpressure and having a leak-rate less than 1.0 mL/minute. Thus, it was the only design that was assigned a +1 value.

It is difficult to assess cyclic life functionality based on only a few concept tests involving hydrostatic pressure. Thus, the two bi-leaflet designs were assigned a score of 0. The parabolic valve design was assigned a score of -1, because in proximal static pressure testing, one of the fins cracked and buckled. This highlighted the vulnerability of this particular design to high pressures. The fins are design features that may not tolerate long-term cyclic pressurization, and may not meet the cyclic life functionality requirements.

All valve concepts were assigned a +1 score for the thrombogenecity requirement. This assignment is primarily based on the material of use. PVA is a material that has low thrombogenecity, and since all three designs will utilize PVA, all designs received a good score. It is important to note that different valve geometries may affect the amount or speed at which potential thrombogenesis may occur. However, the shape of the valve aside, all three designs utilizing PVA should have reasonable thrombogenecity properties.

FINAL DESIGN

The final prosthetic valve design was modeled in Solidworks® v. 2004 CAD software (Solidworks Corporation, Concord, MA). The valve was created with a single leaflet piece, with no orifice. This allowed a post-molding cutting process to create the orifice to ensure that the leaflets coapted and sealed properly. The valve body is shaped like a tube. The inlet and the outlet of the tube are flared outwards to facilitate circumferential sealing (Figure 24). Tube thickness decreases at the inlet and the outlet to minimize the profile of the valve in the vein and to allow the valve ends to conform easier to tortuous venous anatomy. All edges of the valve are smoothened with rounds or surface fillets. This reduces the stress concentrations within the valve, and also is less disruptive to blood flow. The leaflets are thicker at the base where they attach to the tubular body of the valve, and taper to a smaller thickness towards the lumen of the valve. The leaflet thickness is thicker than ideal so that the post-molding cutting process would be feasible by hand.

Novel features

This is the first flexible prosthetic vein valve having two leaflets that seal with significant surface contact area contained within a tube with a flared inlet and outlet to facilitate circumferential sealing. The valve's leaflets are not pre-opened, are non-parabolic in shape, and meet in surface sealing contact, thus creating a robust sealing mechanism. The valve can be manufactured from a single material, in a simple molding operation, and can be implanted by various methods, including stenting, using hooks or barbs, or

suturing techniques. The valve is flexible, unlike stiff cardiac valves containing metal that can erode through a vein wall, and will comply with tortuous venous anatomy. It will adapt to the elliptical cross-section of veins, as well as vein distention. The valve will impose minimal radial stress on vein walls compared to prior art describing radially expanding stiff valves. The valve design is unique by itself, and coupled with a material that has demonstrated low thrombogenecity properties, has potential to perform well in clinical applications.

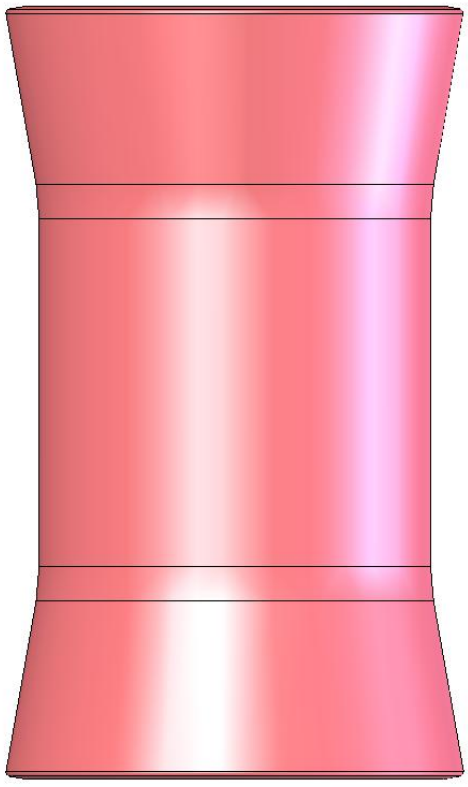


Figure 24: Side view of valve

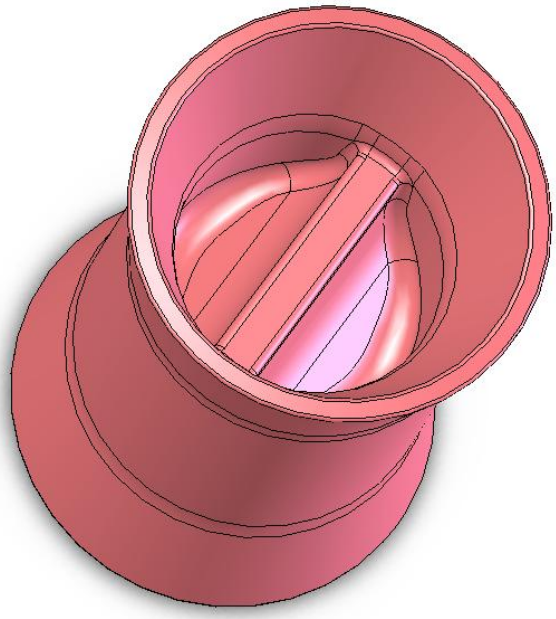


Figure 25: Isometric view of proximal end of valve with leaflets exposed.

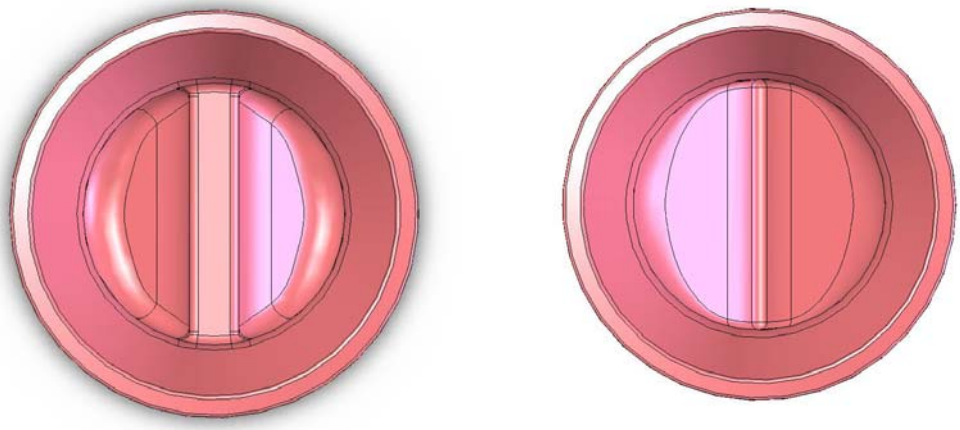


Figure 26: Proximal view, or outlet, of valve (left) and distal view, or inlet, of valve (right), prior to cutting orifice.

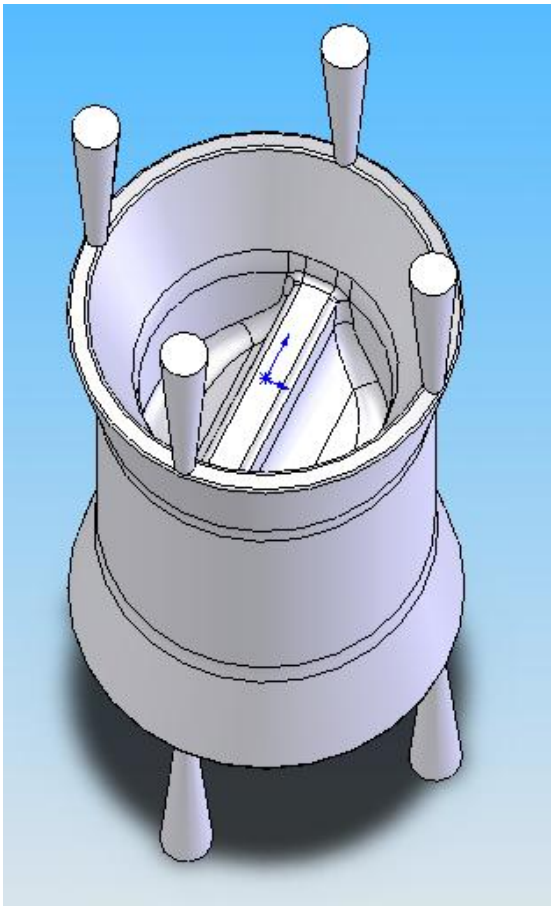


Figure 27: Isometric view of valve die, with gates added to inlet and outlet to facilitate injection molding.

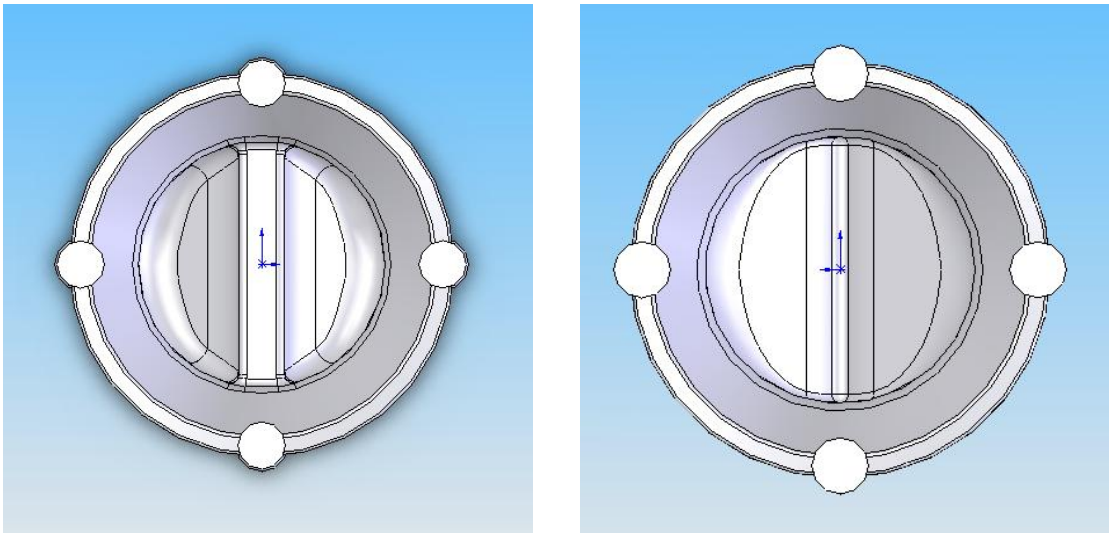


Figure 28: Proximal outlet view of valve die with gates (left) and distal inlet view of valve die with gates (right).

Risk Analysis

In the heavily regulated medical device industry, comprehensive risk analysis is necessary to demonstrate strict design control when developing an implantable medical device. A design tool known as an FMEA, or Failure Modes Effects Analysis, is one method for assessing and mitigating risk. Other risk analysis techniques include FMECA (Failure Modes Effects Criticality Analysis) and FTA (Fault Tree Analysis). Between June 1, 1997, and June 1, 1998, the FDA inspected over 500 medical devices for design controls, and discovered that about 75% of the firms used one or more of these three risk analysis techniques [49]. A FMEA is an effective bottom-up approach for risk analysis, albeit time-consuming. An FTA is used as a top-down approach to risk analysis, and is used by branching out causality modes of an undesired event using logic gates.

Generally, FMEA's are used for Class II and Class III medical devices, which are devices that pose the most risk to the patient in the event of failure. A FMEA organizes the many possible events that could occur during the operation of a product, potentially affecting the functionality of the device and the safety of the consumer. A FMEA examines each risk event with respect to three aspects, severity, occurrence, and detection, and assigns a score to the event for each category. Scoring metrics can be found in Tables 10 - 12. Subsequently, an RPN (Risk Priority Number) is calculated by multiplying the three scores together. This score assesses how severe an event is, how often it could happen, and how easy it would be to detect. The RPN number is then used to prioritize and mitigate risk elements. While there are not any strict metrics used to score each risk

event, for this research an RPN value over 25 was considered to be a significant risk event, warranting corrective action.

A FMEA was used to assess the risk of the valve's design and manufacturing with relation to three main clinical functional modes: valve patency, valve retention, and valve competency (Figures 29-31). This is a brief version of what a true product design FMEA developed at a medical device company would entail. Emphasis was placed on the most patient-critical clinical requirements.

Table 10: Scoring metric for severity of failure [50]

Degree of Severity	**Description**	**Score**
Very High	Death or serious injury likely without prompt medical intervention. Death may be imminent.	5
High	Patient has moderate or chronic clinical symptoms in response to significantly decreased performance and is associated with mild concern for patient safety. (ie., continued severe swelling, ulcerations, severe varicosities, bleeding, dizziness, shortness of breath)	4
Moderate	Patient may present with mild or intermittent clinical symptoms indicative of slightly reduced performance. Patient safety has not been compromised and product continues to function in the intended manner. (ie., some swelling, mild pain, mild varicosities, discomfort)	3
Low	Clinician may have an isolated test finding supporting decreased product performance but patient is asymptomatic. Alternatively, patient may claim symptoms without clinical findings.	2
Very Low	Neither patient safety nor product performance is affected.	1

Table 11: Scoring metric for probability of detecting potential cause of failure [50]

Probability of Detection	Description	Score
Very Low	Patient unaware of product malfunction. Trained clinician unable to detect malfunction. Surgical intervention may be required to detect malfunction.	5
Low	Patient unaware of product malfunction. Trained clinician unlikely to detect malfunction without an ascending or descending venogram	4
Moderate	Patient unlikely aware of malfunction. Clinician may require targeted investigation (Doppler ultrasound, air plethysmography) to discern problem.	3
High	Patient may be aware of malfunction. Clinician aware of malfunction following routine examination.	2
Very High	Patient fully aware of product malfunction. (ie., clinical symptoms present). Alternatively, physician may easily detect malfunction during surgery (Harvey's test)	1

Table 12: Scoring metric for probability of failure occurrence [50]

Probability of Occurrence	Description	Score
Likely	Incidence significantly more than 20%.	5
Probable	Incidence approximately 5-20%.	4
Possible	Incidence approximately 1-5%.	3
Remote	Incidence less than 1%. Occurrence contingent upon implant error, patient anomaly, or other unlikely event.	2
Unlikely	Incidence less than 0.1%.	1

Product:	Prosthetic vein valve				Design FMEA					
Designer:	Rahul Sathe				Potential Failure Mode and Effects Analysis					
#	**Design Function**	**Potential Failure Mode**	**Potential Effect(s) of Failure**	**Sev**	**Potential Causes of Failure**	**Prob**	**Current Design Controls**	**Det**	**RPN**	**Recommended Action(s)**
1	**Valve patency**	Partial Obstruction	Reduced blood flow to heart	4	Leaflet tears and folds, obstructing pathway	2	Hydrostatic, hydrodynamic and burst pressure testing	3	24	None at this time
				4	Valve skews in vein, stopping central flow	1	Valve length-diameter aspect ration > 2	4	16	None at this time
				4	Blood clots in leaflet pockets	3	Proper material selection - preclinical trial	4	48	Histological analysis of valve during animal trial
				4	Blood clots distal to orifice	2	Proper material selection - preclinical trial	4	32	Histological analysis of valve during animal trial
		Full Obstruction	No circulation within leg	4	Leaflets don't open	2	Opening pressure testing, cyclic pressure testing	3	24	None at this time
				4	Blood clots in orifice	3	Proper material selection - preclinical trial	3	36	Histological analysis of valve during animal trial
			Tissue ischemia and hypoxia	4	Leaflets don't open	2	Opening pressure testing, cyclic pressure testing	3	24	None at this time
				4	Blood clots in orifice	3	Proper material selection - preclinical trial	3	36	Histological analysis of valve during animal trial
			DVT formation	4	Leaflets don't open	2	Opening pressure testing, cyclic pressure testing	4	32	Histological analysis of valve during animal trial
				4	Blood clots in orifice	3	Proper material selection - preclinical trial	4	48	Histological analysis of valve during animal trial

Figure 29: Design FMEA for valve patency

Product:	Prosthetic vein valve				Design FMEA					
Designer:	Rahul Sathe				Potential Failure Mode and Effects Analysis					
#	**Design Function**	**Potential Failure Mode**	**Potential Effect(s) of Failure**	**Sev**	**Potential Causes of Failure**	**Prob**	**Current Design Controls**	**Det**	**RPN**	**Recommended Action(s)**
2	**Valve retention**	Valve migration	Valve dislodges and obstructs vein	4	Valve erodes through fixation mechanism	2	Suture pull-out strength calculations	4	32	Functional testing of valve with sutures in place
				4	Sutures break	2	Suture pull-out strength calculations	4	32	Functional testing of valve with sutures in place
				4	Stent did not expand properly	3	None	4	48	Functional testing of stent-delivery
			Death - Valve travels to IVC or right atrium	5	Valve erodes through fixation mechanism	2	Suture pull-out strength	4	40	Functional testing of valve with sutures in place
				5	Sutures break	2	Suture pull-out strength	4	40	Functional testing of valve with sutures in place
				5	Stent did not expand properly	3	None	4	60	Functional testing of stent-delivery

Figure 30: Design FMEA for valve retention

Product:	Prosthetic vein valve			Design FMEA					
Designer:	Rahul Sathe			Potential Failure Mode and Effects Analysis					
#	**Design Function**	**Potential Failure Mode**	**Potential Effect(s) of Failure**	**Sev**	**Potential Causes of Failure**	**Prob**	**Current Design Controls**	**Det**	**RPN**	**Recommended Action(s)**
3	**Valve competency**	Orifice leakage	Distal leg swelling	4	Poor leaflet coaption	3	Proximal, cyclic, and burst pressure	1	12	None at this time
				4	Leaflet damage	2	Proximal, cyclic, and burst pressure	1	8	None at this time
			Varicosities	3	Poor leaflet coaption	3	Proximal, cyclic, and burst pressure	1	9	None at this time
				3	Leaflet damage	2	Proximal, cyclic, and burst pressure	1	6	None at this time
			Continued pain	3	Poor leaflet coaption	3	Proximal, cyclic, and burst pressure	1	9	None at this time
				3	Leaflet damage	2	Proximal, cyclic, and burst pressure	1	6	None at this time
		Circumferential leakage	Distal leg swelling	4	Sutures break	2	Proximal, cyclic, and burst pressure	1	8	None at this time
				4	Stent did not expand properly	3	Proximal, cyclic, and burst pressure	1	12	None at this time
			Varicosities	3	Sutures break	5	Proximal, cyclic, and burst pressure	1	15	None at this time
				3	Stent did not expand properly	5	Proximal, cyclic, and burst pressure	1	15	None at this time
			Continued pain	3	Sutures break	5	Proximal, cyclic, and burst pressure	1	15	None at this time
				3	Stent did not expand properly	5	Proximal, cyclic, and burst pressure	1	15	None at this time

Figure 31: Design FMEA for valve competency

Risk Mitigation

Potential failure events with an RPN score larger than 25 are highlighted in orange as areas of significant risk. Risk events above this threshold require some sort of preeminent action, via testing, further device development, or re-design. RPN scores between 20 and 25 were highlighted in yellow as items that should be noticed as lower risk potential failure modes, but do not require further development or testing at this time.

Failure modes that have RPN numbers below 20 were de-prioritized, having been addressed through prior engineering analysis or testing.

From the FMEA, it is clear that higher risk of failure is associated with valve patency and retention, and not valve competency. The functional tests designed and conducted in this research address act as design controls for many of the potential failure modes. However, for those failure modes having highest levels of risk, there are several additional corrective action items that are recommended to help mitigate risk (Table 13).

Table 13: Mitigation strategies for high risk failure modes

Failure mode	**RPN range**	**Recommended corrective actions to mitigate risk**
Partial obstruction of valve orifice	32-48	Flow studies should be examined with various orifice opening sizes to characterize the valve's inefficiency due to pressure loss. An animal study will help demonstrated the valve's performance with regards to thrombotic occlusions impeding flow. An animal study has been planned for the summer of 2006.
Full obstruction of valve orifice	32-48	An animal study will help demonstrated the valve's performance with regards to thrombotic occlusions impeding flow. An animal study has been planned for the summer of 2006.
Valve migration	32-60	Extensive testing should be carried out to examine implantation and fixation methods for the valve. These tests should include quantifiable data reflecting the pullout strength of sutures, stents, hooks, or barbs in veins. The battery of tests can include mechanical bench testing, *in vitro* studies of the valve implanted into excised veins, cadaver studies, and animal studies.

Because this research concentrates on valve operation after implantation, studying the risk associated with the valve implantation procedure was considered outside of the scope of this work. However, just as a Design FMEA was conducted on the valve's design, a Process FMEA should eventually be conducted on both the manufacturing of the valve, as well as the implantation of the valve. These tools will help identify additional failure modes and high risk events.

VALVE FABRICATION

Valve Die Manufacturing

The prosthetic valves are comprised of 15% poly(vinyl-alcohol) hydrogel, manufactured per U.S. Patent 5,981,826. Valves were fabricated by injecting PVA into a two-part silicone cavity mold, and subjecting the valves to a freeze-thaw curing process.

Using the final CAD designs of the valves, a set of four extrusions was created on both the inlet and the outlet of the valve, to act as gates during the injection molding process. Valve dies (Figure 32) were made using stereolithography (SLA) (Quickparts.com, Atlanta, GA), a rapid-prototyping technique, using STL files derived from CAD files. The material used for SLA was Somos 8110 (DSM Somos, Elgin, Illinois) a semi-flexible plastic material. The resolution of the fabricated valve was 0.013 mm. During rapid-prototyping, the valves were orientated with the longitudinal axis orthogonal to the resin pool during laser curing. This was important for manufacturing the valves, since the construction of the leaflets required a vertical orientation for substrate support. Semi-flexibility was required of the material so that the SLA dies could be removed from the cavity molds without damaging either the dies or the molds.

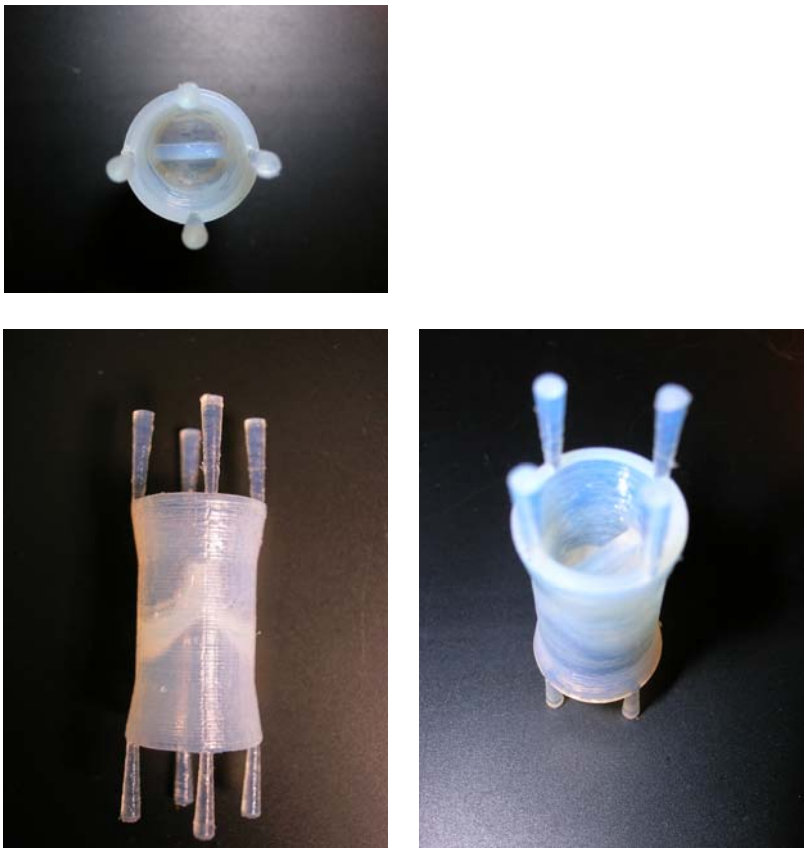


Figure 32: Rapid-prototyped valve die with extrusions for forming injection molding gates

Figure 33: Rapid prototyped valve die without gate extrusions

Mold Manufacturing

The SLA valves acted as the positive die for making two-part cavity molds of the valve. Four silicone cavity molds were made of Sylgard 184®, a silicone elastomer, (Dow Corning, Midland, Michigan). The molds needed to be comprised of a flexible material, so that the SLA dies as well as the PVA valves could be removed easily. Silicone was used as mold material for its elastic properties, its biocompatibility, and its transparency. Prior to pouring molds around the SLA valves, the SLA valves were coated with a thin layer of 5% PVA solution, with each coat allowed to air dry for approximately 4 hours. This thin coating was required to prevent a phenomenon known as inhibition from occurring to the silicone. Inhibition is an event that involves poor curing of a two-part silicone material. When exposed to certain plastics, silicone may not cure, and such was the case with Somos 8110. The thin coating of PVA prevented this problem. The coating did not significantly alter the dimensions or tolerances of the valve. In fact, the coating smoothened out the miniscule ridges that result from SLA resin layering, minimizing the effect of sharp edges on the valve.

The coated SLA valves were placed in plastic mold wells. The mixed silicone was poured around the SLA dies until it reached about three fourths of the height of the SLA dies. To remove the large air pocket underneath the die's cusps, the die was grasped and angled with forceps while in the liquid silicone mixture to allow the air bubble to float out. A vacuum of 0.06 MPa gauge was applied for about 5 minutes to remove air bubbles from the silicone. Subsequently, the molds were allowed to cure at ambient temperature for 12 hours, and then cured in an oven at 37 °C for 3 hours. After cooling, a

thin film of mold release agent was applied on the top of the silicone half to facilitate mold separation, and allowed to dry for 30 minutes. The silicone pouring and curing process was then repeated for creating the top half of the mold. The plastic mold well was cut and removed, and the mold halves were gently pulled apart, exposing the valve dies for removal.

Figure 34: All four silicone molds with rapid prototyped valve dies.

Injection Molding

Test valves were created by injecting liquid 15% PVA solution at approximately 80 °C temperature into the silicone mold with a 60 cc syringe. The PVA was injected into the gates on the bottom of the mold. Warm temperatures reduced the viscosity of PVA

solution, and made injection molding much more manageable. It was observed that higher pressure and velocity of injection aided in distributing the solution throughout the mold cavity, and reduced air-bubble presence in the finished product. The seven open gates on each valve allowed air to vent from the cavity as PVA was injected into the eighth gate.

Valve Curing: Freeze-Thaw cycles

The PVA valves were cured via a freezing and thawing process, effectively cross-linking the polymer to create a solid gel. One freeze-thaw cycle consisted of freezing the molds containing PVA for 12 ± 0.5 hours at -15 °C. The molds were then removed from the freezer and were left to thaw at ambient conditions for 3 ± 0.5 hours. The molds wer loosely wrapped in damp cloth to prevent the hydrogel from drying. Each successive freeze thaw cycle increased the number of cross-links within the hydrogel, thereby increasing its bulk elastic modulus. Hydrogels generally swell in the presence of water, and if not stiff enough, will collapse and deform under its own weight. Thus, the valves were kept within the molds during each freeze-thaw cycle to maintain dimension and form.

Valve Removal and Final Processing

After the molds were thawed sufficiently, the mold halves were gently pulled part, exposing the valves and the flash created during manufacturing. Flash is excess material on a molded part formed because of mold gates or parting lines. The valves were

removed very carefully from the molds by using light pulsed air pressure applied to the gates to pop the valves loose. Excess flash was trimmed carefully, and valves were selected from each batch of 16 for their quality. Quality was assessed primarily based on porosity, holes, completed parts, and homogeneity of the material. Part rejection rate was approximately 25%.

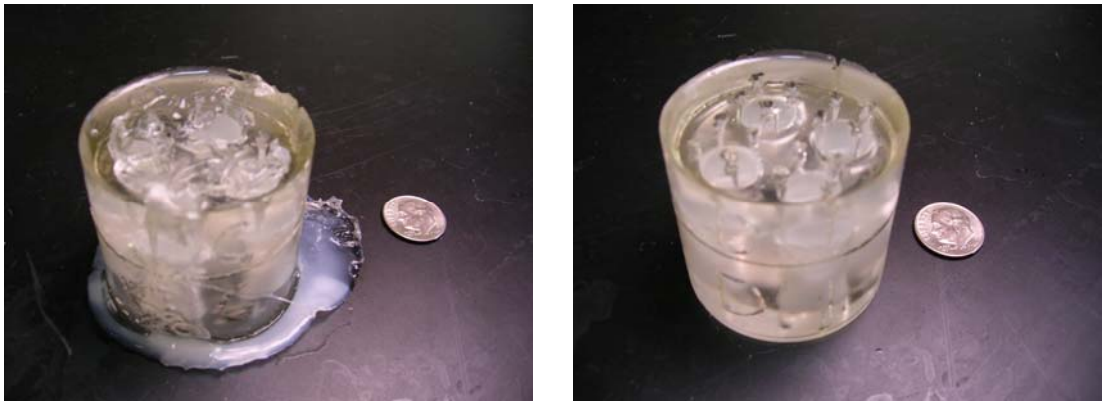


Figure 35: Silicone mold with excess PVA flash (left). Silicone mold with flash removed (right); note that the mold contains 4 cavities for fabricate 4 valves at the same time. The white translucent cylindrical objects within the mold are the valves.

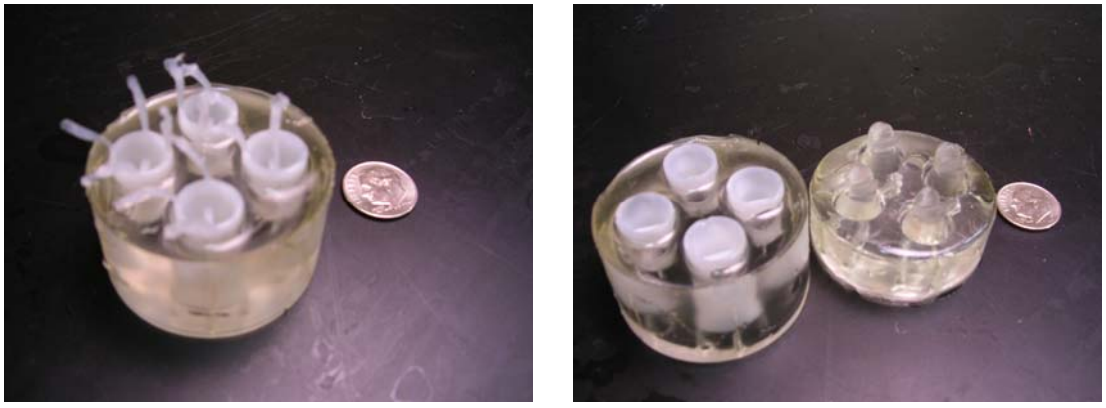


Figure 36: Silicone mold with top half removed, exposing the valves and flash (left). Silicone mold halves with flash removed from valve ends (right).

Figure 37: Silicone mold halves with valves, top view (right). Silicone mold halves with valves, side view (right).

Figure 38: Silicone mold half with valve removed, top view (left). Silicone mold half with three valves; note the leaflets are joined and do not have an orifice (right).

For selected valves, the orifice was cut open with surgical scissors, to thus transform the sealed valve into a bi-leaflet valve (Figure 39). This was a critical step in fabricating a functioning valve. The cutting techniques were practiced on about 20 scrapped valves to obtain consistency. The function of the valves depended significantly on the accuracy and quality of cut. True quality of cut could not be easily assessed without functional testing, thus screening of valves for testing occurred during initial testing. Valves that were assessed to be potentially functional were stored in the molds to retain dimensions, and the molds were submerged in a water bath to keep the hydrogel moist.

Figure 39: Surgical scissors were used to cut the orifice. The cutting process took about 5 minutes per valve.

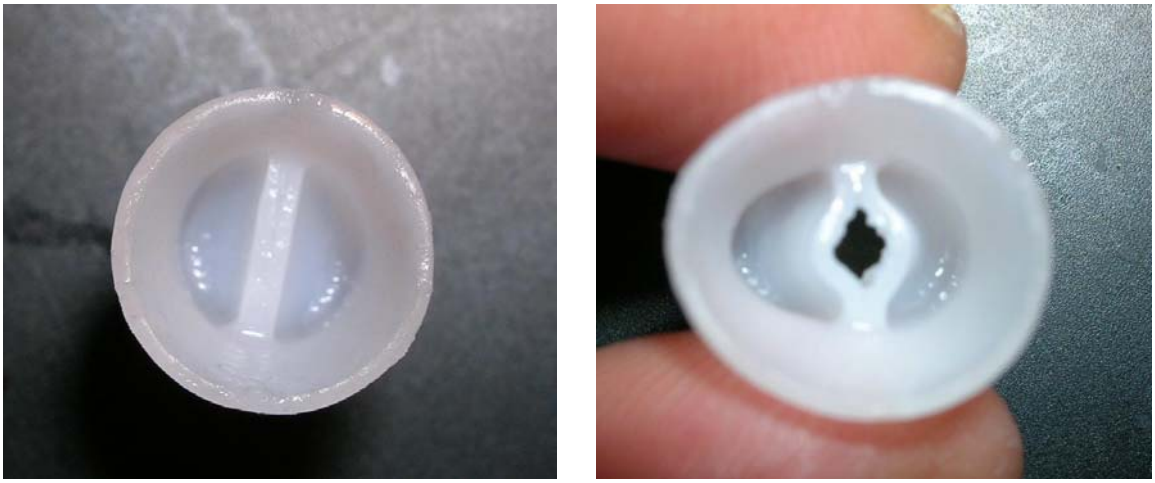


Figure 40: Valve in the close position (orifice has already been cut); note the faint line along the center of the valve where the leaflets meet to seal (left). Valve in the open position, revealing the orifice (right).

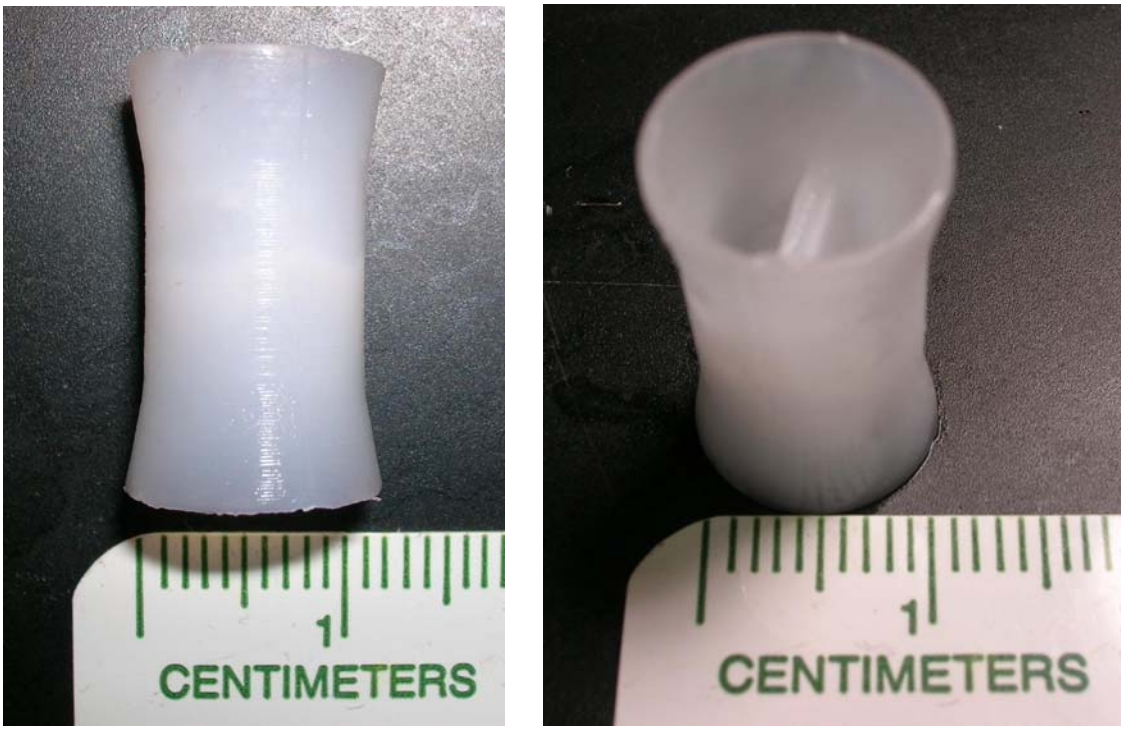


Figure 41: Side view of the valve, revealing its flared inlet and outlet for better circumferential sealing (left). Isometric view of the valve; separate leaflets are distinguished by the orifice line (right)

Vein-like Tube Fabrication

A flexible prosthetic valve must accommodate the dynamic environment of native veins. A vein-like tube was needed to provide an appropriate test environment for the valve, and to mimic vein mechanics during physiologic loading. It was important to re-create sinus expansion and vein distention proximal to the valve during applied proximal pressure. A 15% PVA hydrogel was used as the material of choice for this particular test application. Various other materials were considered for flexible tube test beds, including silicone elastomers, Tigon ® tubing, and excised distal porcine vena cava. In feasibility fabrication, silicone tended to be too brittle, and was difficult to extract from molds without becoming damaged. Tigon tubing was too stiff, which prevented any noticeable sinus expansion at low applied pressure. Porcine vena cava were excised from adult farm

pigs (Holifield Farms, Porterdale, Georgia) at an abattoir, within 20 minutes of death. However, the vein samples were not ideal for cyclic testing, since biologic veins tend to retain reasonable mechanical properties for only a few days; and cyclic testing would last over five days.

The hydrogel tubes had a 10 mm inner diameter, a 12 mm outer diameter, and a 1 mm thickness. The tubes were made by pouring 15% poly(vinyl-alcohol) solution into machined molds with end-caps, and undergoing one freeze-thaw cycle. The tubes were approximately 7 cm long, and were examined closely for porosity, gross non-uniformity or in-homogeneity before used in testing.

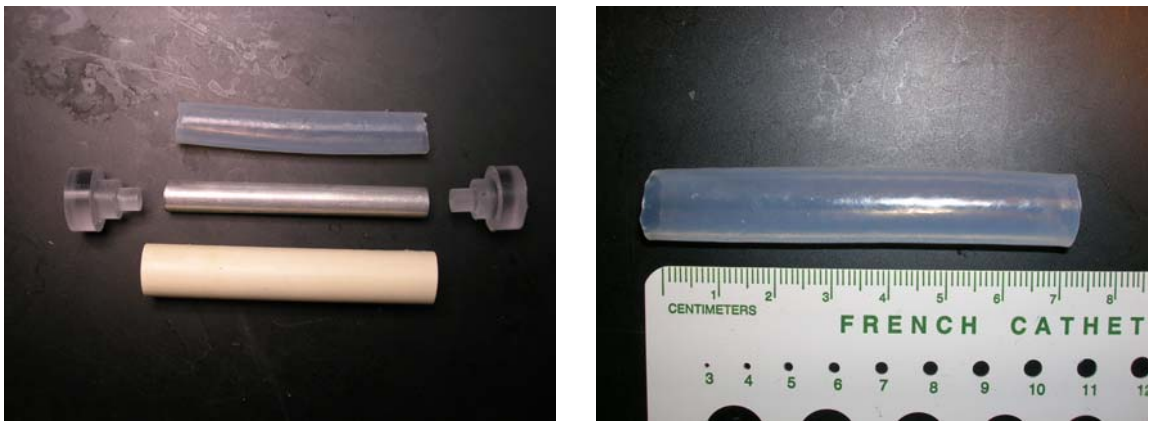


Figure 42: Exploded view of tube (translucent cylinder) and the mold components used to make the tube (left). Vein-like tube after one freeze-thaw cycle (right)

Fixation of Valves in Tubes

The valves needed to be fixed into the vein-like tubes in a manner simulating an implanted prosthetic valve. Ideally, an implanted prosthetic valve would promote some degree of intimal formation from the vein, such that tissue would grow into the outer

periphery of the valve, similar to in-growth for Dacron ® vascular grafts. (while PVA generally doesn't elicit an intimal response, Dacron® could be integrated into the periphery of the valve to promote tissue growth. Appropriate tissue in-growth does two main things for a vascular prosthetic. First, it secures the prosthetic in place and prevents migration. Second, it seals the outer circumference of the prosthetic, so that blood flow will be channeled primarily only though the intended orifice.

Thus, for testing, the valves needed to be fixed in a manner that secured the valves in the tube, yet also prevented circumferential leaking. This was accomplished by using liquid 15% PVA solution as glue. The viscous solution was applied by brush into the lumen of the tube at ambient temperature. The valve was placed inside and positioned appropriately, and additional solution was applied at the line joints where the valve inlet and outlet interfaced with the tube wall (Figure 43). Tubes containing valves were then subjected to two freeze-thaw cycles (Figure 44), and the valves were effectively fixed in place and ready for testing. The test specimens were stored in pink dyed water in plastic vials prior to testing (Figure 44). The pink color provided greater contrast for visually inspecting the valve's leaflets inside the tube. Hereafter, tubes containing valves will be referred to as test specimens.

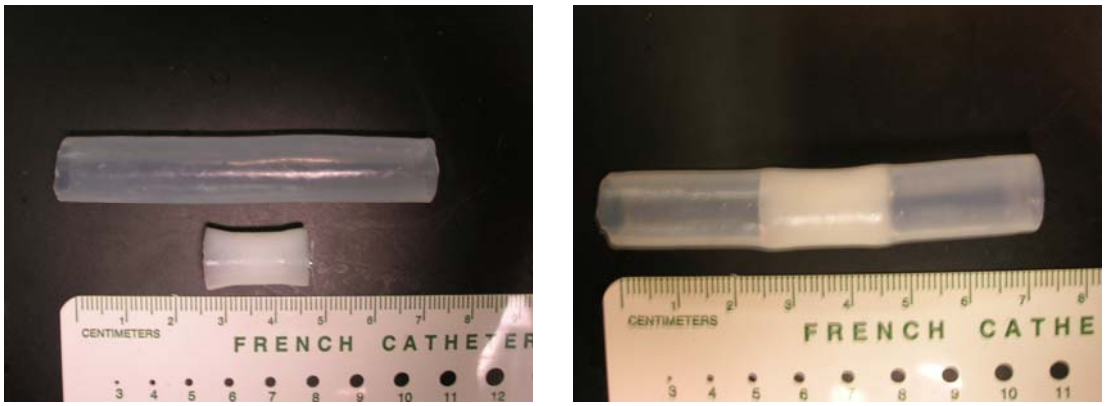


Figure 43: Vein-like tube and valve (left). Valve inserted into vein-like tube, and fixed with 15% solution of PVA (right).

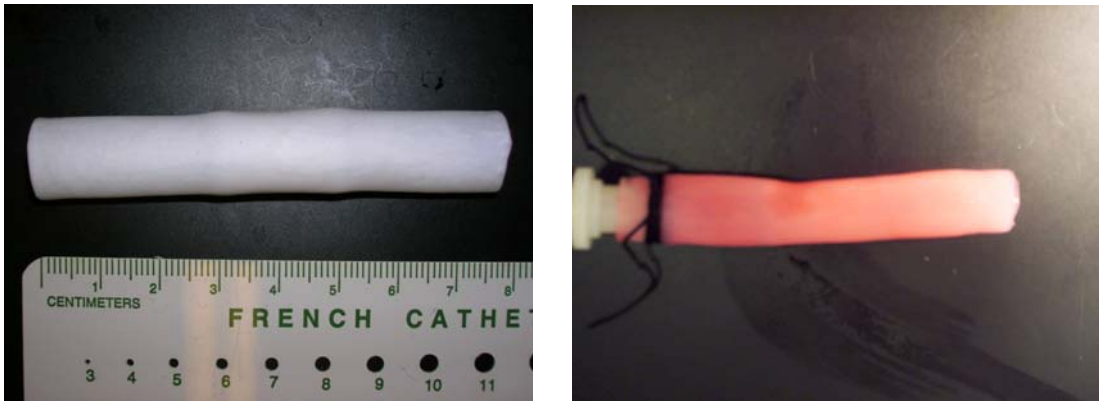


Figure 44: Test specimen after 2 additional freeze thaw cycles, still in frozen state (left). Test specimen tied onto fitting for pressure testing, after completely thawing, and being dyed pink (right).

TEST PROTOCOL

Test specimens of both 3 freeze-thaw and 5 freeze-thaw cycles were subjected to the same test protocol. Tests were performed specifically to evaluate the valve based on critical design specifications. To summarize, design criteria included that the valve:

1) open with a distal pressure gradient less than 5 mmHg,

2) withstand backpressure of 300 mmHg with less than 1.0 mL/min of leakage, and

3) withstand 500,000 cycles of opening and closing while meeting or exceeding design specifications 1 and 2.

Table 14 briefly describes the various tests (detailed methodology is found in subsequent text). Figure 45 describes in a flow chart the general test protocol for evaluating valve functionality.

Table 14: Brief description of function tests and their purposes

Functional Test	Purpose
Test A Initial Opening Pressure	This test evaluates what distal pressure gradient is required to open the valve leaflets and allow antegrade (forward) flow.
Test B Reflux Leakage	This test evaluates what amount of leakage, if any, the valve allows when proximal pressure is applied.
Test C Second Opening Pressure	This test is performed in the same manner as Test A. However, this test examines the effect of high sustained backpressure on the valve's ability to open again.
Test D Cyclic Life Functionality	This test evaluates the valve's cyclic life functionality by opening and closing the valve in physiologically-simulated conditions thousands of times.
Test E Burst Pressure	This test demonstrates the proximal pressure at which the valve will fail and cause excessive leakage.
Failure analysis	This analysis consisted of a qualitative approach for examining failure modes in valves that did not meet design criteria. This analysis was conducted primarily for valves that failed Tests A and B and valves that underwent Test E. However, analysis was performed on a few good valves as well, to compare qualitatively good valves to bad valves.

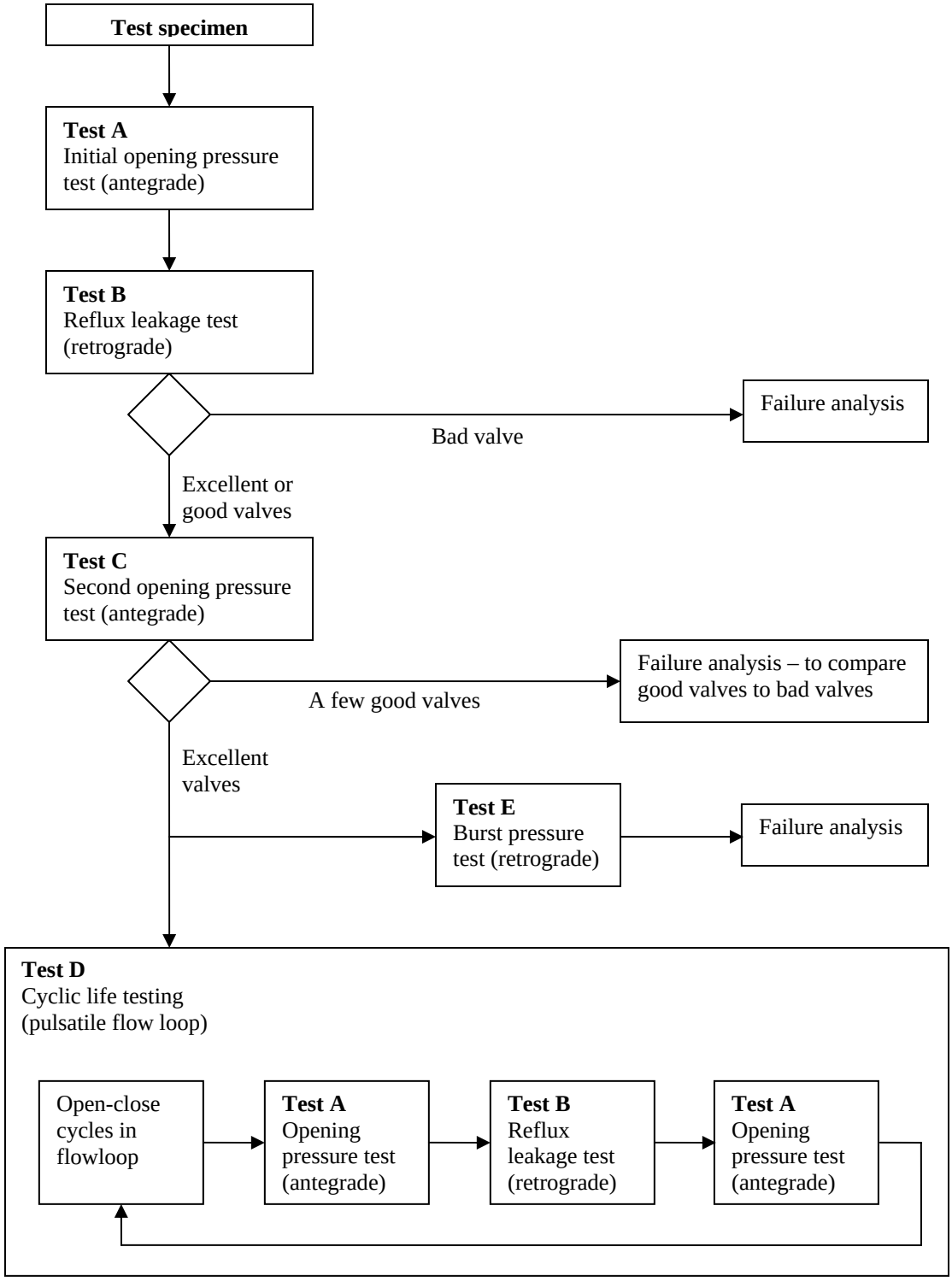


Figure 45: General flow process for functional tests

Flow Media Selection

Water was used as the test media. Since bulk pressure was the parameter of primary concern for all three design criteria, the impact of viscosity on valve performance was considered negligible in this research. Unlike glycerol-water mixtures that are often used to mimic blood's viscosity and density, plain water facilitated easier cleanup of the valve and flow-loop. Additionally, since vein valve operation is primarily pressure-driven and not flow driven [20, 51], water was a reasonable medium to use for testing. During all hydrostatic and hydrodynamic testing, the specimens were kept wet with moist cloth, to prevent the hydrogel from drying.

Preparation for Test A (Opening pressure) and Test B (Reflux Leakage)

Test specimens were placed in a flow setup with a hand-operated syringe pump to evaluate valve performance for design criteria 1 and 2. For all hydrostatic testing, the test specimens were orientated horizontally, at the same height as the pressure transducer and syringe pump, to negate the effects of gravity on pressure readings. The leaflets were orientated so that the commissural line was orthogonal to the plane of the table that tests were conducted on. A pressure transducer (Harvard Apparatus, South Natick, Massachusetts) was placed in line with the syringe and specimen, and was calibrated periodically with a hydrostatic water column. During testing, hand-syringe techniques were used to apply proximal and distal hydrostatic pressure to the specimens. Constant applied pressure was needed in order to effectively measure the valve's functional performance. Valve performance varied with manufacturing quality, and a hand-syringe

pump technique created an effective controlled method to maintain this constant applied pressure. Techniques were practiced prior to testing to achieve consistency and accuracy.

Test A – Initial Opening Pressure Test

Opening pressure was measured first, using dyed water for better leaflet visualization. The test specimens were secured onto a plastic fitting by tying a 2-0 Vicryl suture (Ethicon, Inc, Somerville, NJ). A rubber o-ring was present between the plastic fitting and specimen tube. The specimen was orientated such that the distal end of the valve was closest to the syringe, and the proximal end was facing the ambient atmosphere (Figure 46). Pressure was applied using the hand-operated syringe in 1 mmHg increments, and held for approximately 5 seconds at each increment. During pressurization, the valve was monitored for the instance of valve opening. Valve opening was defined as occurring when dyed water became first noticeable on the proximal side of the leaflets, and the pressure was recorded when this event occurred. After each opening, pressure was reduced to 0 mmHg, and water was removed from the proximal portion of the specimen with a pipette and absorbent cloth. Five independent measurements were taken for opening pressure, one minute apart from each other. One minute was allowed to pass between each measurement to relieve the valve of viscoelastic effects from the prior test. Opening pressure testing occurred before testing for reflux leakage, and then again afterwards, to quantify any functional differences from the valve experiencing high backpressure.

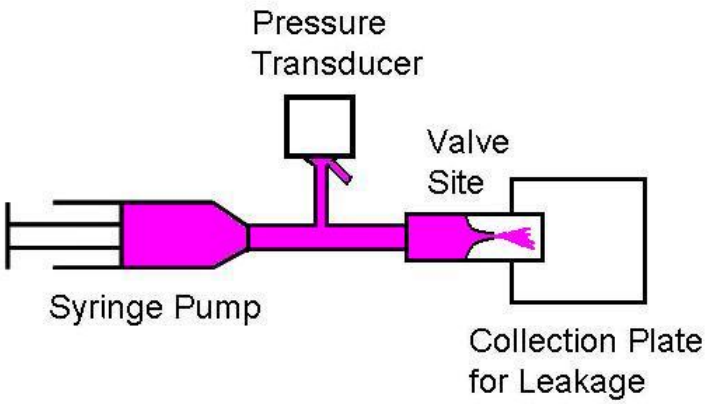


Figure 46: Diagram of hydrostatic pressure test-setup for testing opening pressure (top view)

Test B - Reflux leakage

Reflux leakage was measured by applying proximal pressure on the valve and measuring the volume of water that leaked through the leaflets. For this test, the specimen was reversed in orientation in the setup. The proximal end of the valve faced the syringe pump, and the distal end was exposed to the ambient atmosphere (Figure 47). An 18 mm inner diameter clear plastic tube was placed around the specimen to restrict its diameter distention to only 1.5 times its original diameter. This was done to mimic venous distention, since veins distend to about 1.5 to 1.6 times their original diameter in vivo [12, 13]. Proximal pressure was applied from 0 mmHg to 300 mmHg, in increments of approximately 18 to 20 mmHg. At each pressure step, pressure was applied in a ramp fashion from 0 mmHg to the desired step condition in a span of 5 seconds, and then held at a constant value for a total duration of 30 seconds. Leakage was collected in a non-wettable container, and measured using a 2.5 cc medical-grade syringe with needle to gather the water droplets. This was an effective process for ensuring that all the leakage

was collected for measurement. Approximately one minute elapsed between testing at each pressure step. One minute was allowed to pass between each measurement to relieve the valve of viscoelastic effects from the prior test.

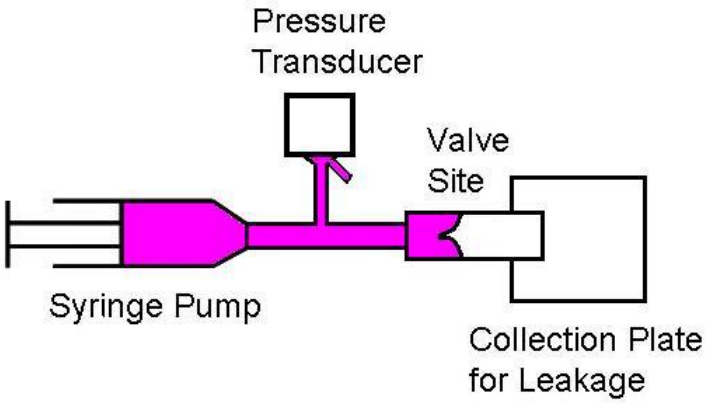


Figure 47: Diagram of hydrostatic pressure test-setup for testing proximal pressure and reflux leakage (top view)

From these measurements, a leak-rate value for each pressure level could be calculated, with units of mL/minute. As opposed to one minute, a test duration of 30 seconds was used for measuring leak-rate because it was practical and did not sacrifice the quality of valve assessment. At high pressures, the vein-like tube would expand considerably in diameter. This caused much of the water volume in the syringe pump to be transferred to the newly expanded volume of the test specimen. Because the syringe pump was limited in capacity to 10 cc, excessive leakage of low-performing valves would result in the remaining syringe volume being drained before one minute could surpass. A larger capacity syringe would solve this problem; however, a larger syringe would also result in

less control in maintaining constant pressure, a critical requirement for testing. Thus, it was more reasonable to use 30 seconds as the duration of the proximal pressure test.

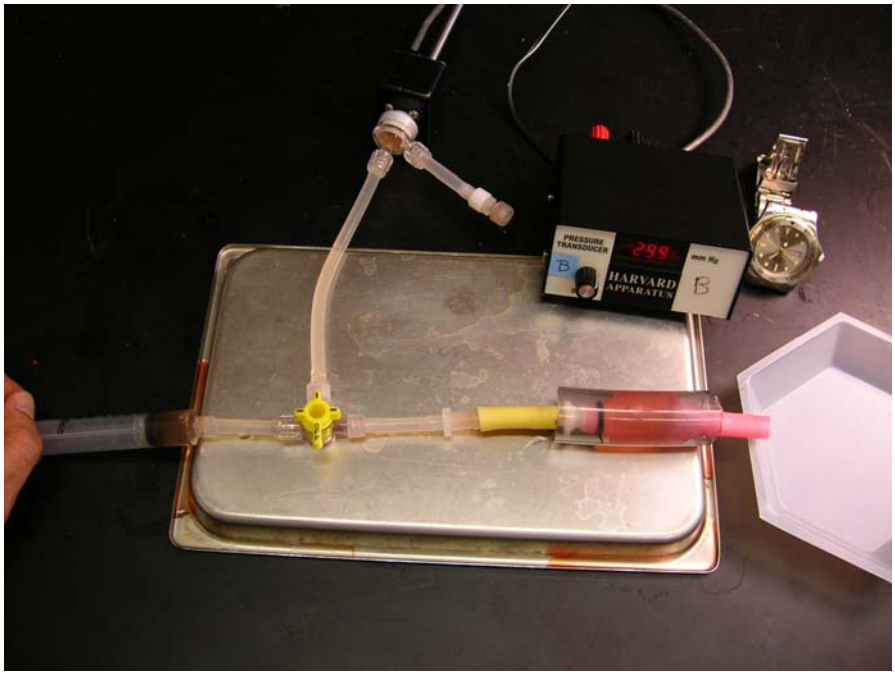


Figure 48: Hydrostatic pressure test-setup for testing proximal pressure and reflux leakage. Specimen shown is B3-8-T9, exposed to approximately 300 mmHg of proximal pressure with no leakage present. An 18 mm inner diameter clear plastic tube was placed around the specimen to limit its distention to a physiologically relevant diameter.

Figure 49: Test specimen B3-8-T9 exposed to approximately 300 mmHg of proximal pressure with no leakage present. Note the 18 mm plastic tube used to limit the sinus distention to only 1.5 times the original diameter. The valve site is to the right of the sinus bulge.

Test C – Second Opening Pressure Test

After exposing the valve to high proximal pressures during the proximal pressure test, the valve's opening pressure was again evaluated. This test was conducted to characterize any change in the valve's performance after being exposed to severe pressure conditions. Because PVA is a viscoelastic material, it was important to observe the effects of high proximal pressure loading on the valve's ability to still open at low pressure gradients. Each second opening pressure test was performed within 3 minutes of completing the proximal pressure test. The second opening pressure test was required for all valves that demonstrated good or excellent proximal pressure test results. It was not performed or required for valves that were deemed bad. Valves that had high leakage had problems of

leaflet coaption, and this would make the opening pressure of the valve seem lower than it should have been. The same setup for Test A, the initial opening pressure test, was used for this test.

Test D – Cyclic Life Testing

After initially evaluating the valve's hydrostatic performance, the test specimen was placed in a cyclic flow loop, designed to open and close the valve numerous times in simulated physiologic conditions. The specimen was tied in place with 2-0 Vicryl sutures and placed in a water bath, and covered with absorbent paper cloth. The water bath and paper cloth kept the hydrogel specimen from drying over the course of the days cyclic testing would occur. The valve was orientated such that the proximal end was facing upwards, exposed to the pressure of the water column above it, thus mimicking a leg vein valve (Figure 50).

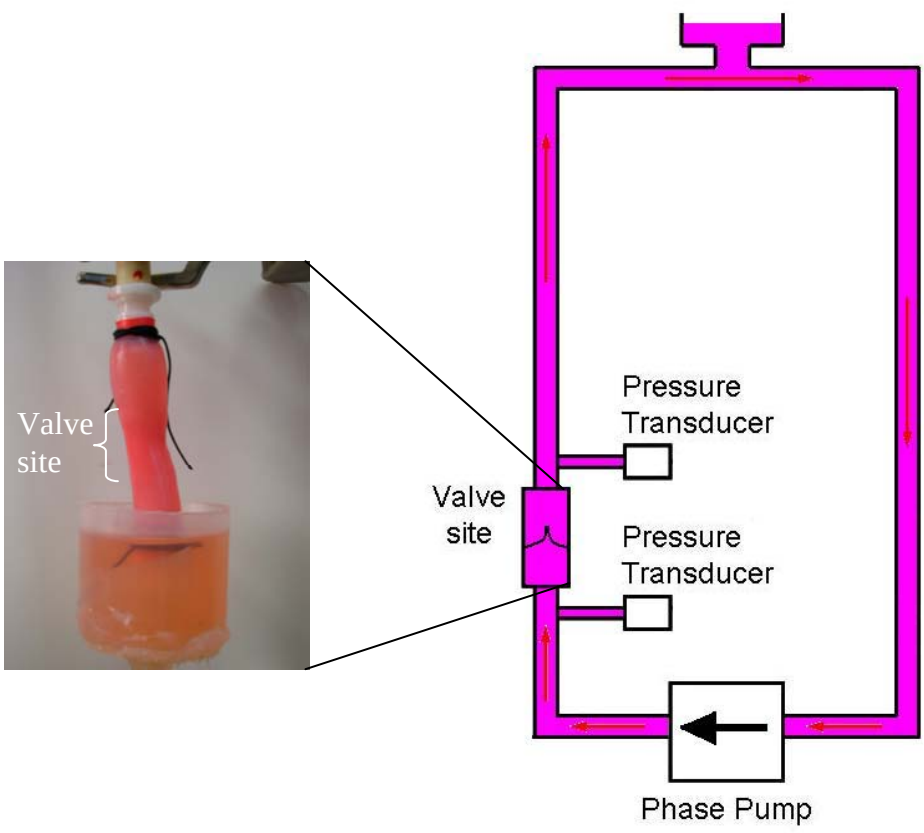


Figure 50: Hydrodynamic flow loop for evaluating cyclic life functionality (right). Close-up view of test specimen in water bath, without absorbent cloth.

Physiologically, native vein valves open and close synchronously with calf muscle contractions. During normal walking, calf compression propels 10 to 20 mL of blood through the veins, and compression occurs about 40 times a minute (0.67 Hz) during normal cadence [8, 9]. The primary requirement during cyclic testing was that the valve opened and closed in a periodic, identifiable fashion. Correspondingly, multiple Masterflex ® Easy-Load ® rotary phase pumps were placed in parallel, using 24 gauge (8.0 mm) silicone tubing (Masterflex, Cole-Parmer Instrument Company, Vernon Hills, IL), to displace a total of approximately 10 mL of water with each stroke through the valve orifice, at a frequency of 0.70 ± 0.03 Hz. These parameters are consistent with the

frequency and volume of blood flow during calf compression in normal walking cadence. The total net flow of water was 450 ± 30 mL/min. The velocity of the water was not of primary concern in this research, since the aims of this research were to demonstrate pressure functionality of the valve.

The flow loop was designed so that hydrostatic pressure was maintained proximal to the valve at 50 ± 5 mmHg, similar to physiologic conditions proximal to an adult common femoral vein. Tested specimens were evaluated for functional performance at various points during the cyclic testing, generally every 50,000 to 60,000 cycles (about 24 hours). Nearly 1.5 hours were required to remove the valve from the setup, test for opening pressure and reflux leakage, and place the valve back into the setup, and it was reasonable from a time standpoint to only evaluate the valve every 24 hours. At each measurement interval, the test specimen was removed from the loop and exposed to hydrostatic testing. This testing quantified the valve's functionality with respect to reflux leak-rate performance and opening pressure characteristics at various stages of life cyclic testing.

Test E – Burst Pressure Testing

Burst pressure testing characterized the maximum pressure at which valves would remain competent, prior to excessive leakage or structural damage. Burst pressure testing was only conducted on valves that demonstrated functionality in prior hydrostatic testing. A total of 5 valves underwent burst pressure testing. Each specimen slated for this test was placed into the same hand-operated syringe pump setup used for testing reflux leakage.

An 18 mm inner diameter tube was placed around the specimen to restrict its diameter distention to only 1.5 times its original diameter. The specimen with restrictive tube was inserted into the mouth of a clear flask orientated horizontally. The flask was included in the setup to collect water during valve blowout (Figure 51).

Figure 51: Test setup for burst pressure testing was similar to hydrostatic proximal pressure testing, with an addition of a glass flask to contain bursting water.

The valve was pressured at a rate of approximately 50 mmHg per second. A fast rate of pressurization was used to examine how the valve would respond to this type of loading. Fast pressurization occurs in humans during a sudden transition from sitting to standing, or during exercise. Thus, burst pressure testing attempted to mimic this loading. A mechanical syringe pump was not used in this case because existing equipment would not apply proximal pressure at a fast enough rate.

A digital camera was used to record video footage of the test specimen and pressure transducer reading simultaneously. Of the five valves that were pressurized, video recording was only available for four. Each video was later analyzed to determine the pressure at which water first leaked from each test specimen. After valve failure, the specimens were inspected to determine the specific mode of failure.

Failure Analysis

Qualitative failure analysis was conducted to determine the failure mode of valves that did not demonstrate functionality during initial testing. The valve leaflets were of primary concern during failure analysis, as they were the most critical design features that affected the pressure performance of the valve. Failed specimens were dissected to expose the leaflets for visualization. Each specimen tube was cut in the longitudinal direction (similar to a venotomy) from end to end, along the plane of leaflet coaption. The tubes were then spread open on a wax board. Several drops of dilute red dye was applied to the exposed leaflets and allowed to soak into the hydrogel for 10 seconds before being wiped away. This provided greater contrast in the hydrogel for better visualization of surface roughness, pitting, or other defects. Digital pictures were taken of the leaflets for recording visible structural defects.

CHAPTER 3

RESULTS

REVIEW OF TEST PROCEDURES

Five tests were conducted to determine if the prosthetic vein valve met the critical design specifications for bench testing. These criteria are summarized in Table 15.

Table 15: Summary of critical design specifications

Specification Number	Parameter	Design Specification
1	Patency	The pressure gradient required to open the valve and cause forward fluid flow must be less than 5 mmHg.
2	Competency	Valve must structurally bear at least 300 mmHg of static pressure and must not leak more than 1.0 mL/minute for all tested pressure from 0 to 300 mmHg.
3	Cyclic life functionality	The valve must open and close in simulated physiologic conditions for at least 500,000 cycles, and continue to meet design specifications 1 and 2 at all test intervals.

Table 16: Summary of the tests conducted

Functional Test	Purpose
Test A Initial Opening Pressure	This test evaluates what distal pressure gradient is required to open the valve leaflets and allow antegrade (forward) flow.
Test B Reflux Leakage	This test evaluates what amount of leakage, if any, the valve allows when proximal pressure is applied.
Test C Second Opening Pressure	This test is performed in the same manner as Test A. However, this test examines the effect of high sustained backpressure on the valve's ability to open again.
Test D Cyclic life functionality	This test evaluates the valve's cyclic life functionality by opening and closing the valve in physiologically-simulated conditions thousands of times.
Test E Burst pressure	This test demonstrates the proximal pressure at which the valve will fail and cause excessive leakage.
Failure analysis	This analysis consisted of a qualitative approach for examining failure modes in valves that did not meet design criteria. This analysis was conducted primarily for valves that failed Tests A and B and valves that underwent Test E. However, analysis was performed on a few good valves as well, to compare qualitatively good valves to bad valves.

TEST A (OPENING PRESSURE) RESULTS

Table 17: Opening pressure test results for 3 freeze-thaw cycle valves

Freeze-thaw Cycles	Valve Specimen	Test A: Initial Opening Pressure (mmHg)	Test B: Proximal Pressure Testing (mmHg)	Test C: Opening pressure after reflux testing (mmHg)
3	**B1-8-T9**	**2.6 ± 0.7**	**Excellent**	**3.7 ± 0.7**
3	**A3-8-T9**	**3.7 ± 0.7**	**Excellent**	**4.5 ± 0.7**
3	**D1-7-T8**	**2.3 ± 0.7**	**Excellent**	**5.0 ± 0.7**
3	**B2-8-T9**	**3.3 ± 0.7**	**Excellent**	**7.3 ± 1.0**
3	**B3-8-T9**	**2.4 ± 0.7**	**Good**	**8.5 ± 1.3***
3	A4-8-T9	3.0 ± 0.5	Bad	Not tested
3	A1-8-T9	2.6 ± 0.7	Bad	Not tested
3	C2-7-T8	1.4 ± 0.7	Bad	Not relevant
3	D2-7-T8	1.6 ± 0.6	Bad	Not relevant
3	C1-7-T8	2.0 ± 0.5	Bad	Not tested
3	A2-8-T9	2.2 ± 0.7	Bad	Not tested

*Valve experienced 400 mmHg of backpressure prior to second opening pressure test, and thus was not used in average calculation of opening pressure after reflux presented in the summary

Table 18: Opening pressure test results for 5 freeze-thaw cycle valves

Freeze-thaw Cycles	Valve Specimen	Test A: Initial Opening Pressure (mmHg)	Test B: Proximal Pressure Testing (mmHg)	Test C: Opening pressure after reflux testing (mmHg)
5	**D1-9-T10**	**3.7 ± 0.7**	**Excellent**	**4.5 ± 0.7**
5	**C4-9-T10**	**2.8 ± 0.7**	**Excellent**	**4.0 ± 0.9**
5	**C2-4-T5**	**4.1 ± 0.7**	**Excellent**	**Not tested**
5	**C1-9-T10**	**2.0 ± 0.5**	**Good**	**3.7 ± 0.7**
5	**B3-9-T10**	**2.0 ± 0.5**	**Good**	**6.9 ± 0.7**
5	**D3-4-T5**	**3.9 ± 0.7**	**Good**	**Not tested**
5	**B1-4-T6**	**6.4 ± 1.8**	**Good**	**9.4 ± 1.1**
5	C1-4-T5	5.1 ± 0.6	Bad	Not tested
5	A2-4-T6	6.0 ± 0.9	Bad	Not tested
5	D3-9-T10	2.6 ± 0.6	Bad	Not tested
5	D4-9-T10	2.4 ± 0.6	Bad	Not tested
5	D2-9-T10	3.3 ± 1.0	Bad	Not tested

TEST B (REFLUX LEAKAGE) RESULTS FOR 3 FREEZE-THAW CYCLE VALVE

Figures 52 - 62 depict the reflux leak-rate performance during proximal pressure testing for individual valves fabricated using 3 freeze-thaw cycles. Leak-rates were recorded from 0 mmHg to 300 mmHg. In cases where leak-rate exceeded 2.0 mL/min, the test was terminated, and leak-rate data was not acquired at higher pressures. The design requirement for proximal pressure performance was that the valve does not exceed 1.0 mL/min of reflux leakage at any applied proximal pressure from 0 to 300 mmHg. Excellent valves were valves having leak-rates equivalent or less than 0.5 mL/min. Good valves were valves that had leak-rates that met the design criteria. Bad valves had leakage greater than the design criteria.

Table 19: Description of categorizing valve competency

Valve Categorization	Description of criteria
Excellent	Leak-rate $\leq$ 0.5 mL/min
Good	0.5 mL/min < Leak-rate $\leq$ 1.0 mL/min
Bad	Leak-rate > 1.0 mL/min

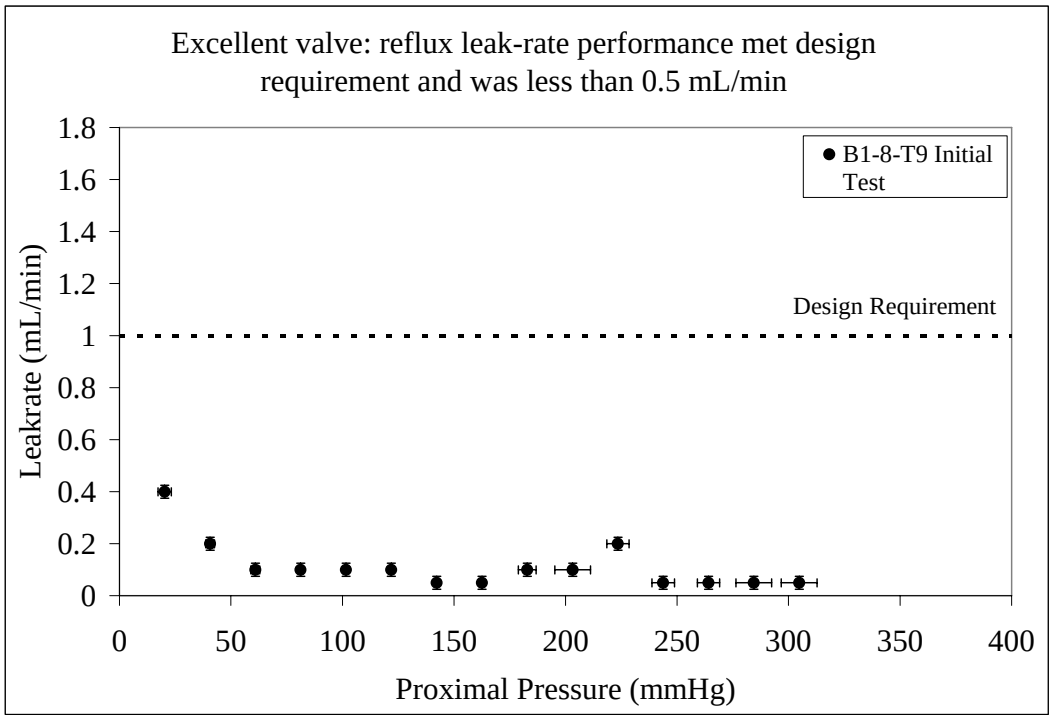


Figure 52: Competency assessment of 3 cycle valve (B1-8-T9)

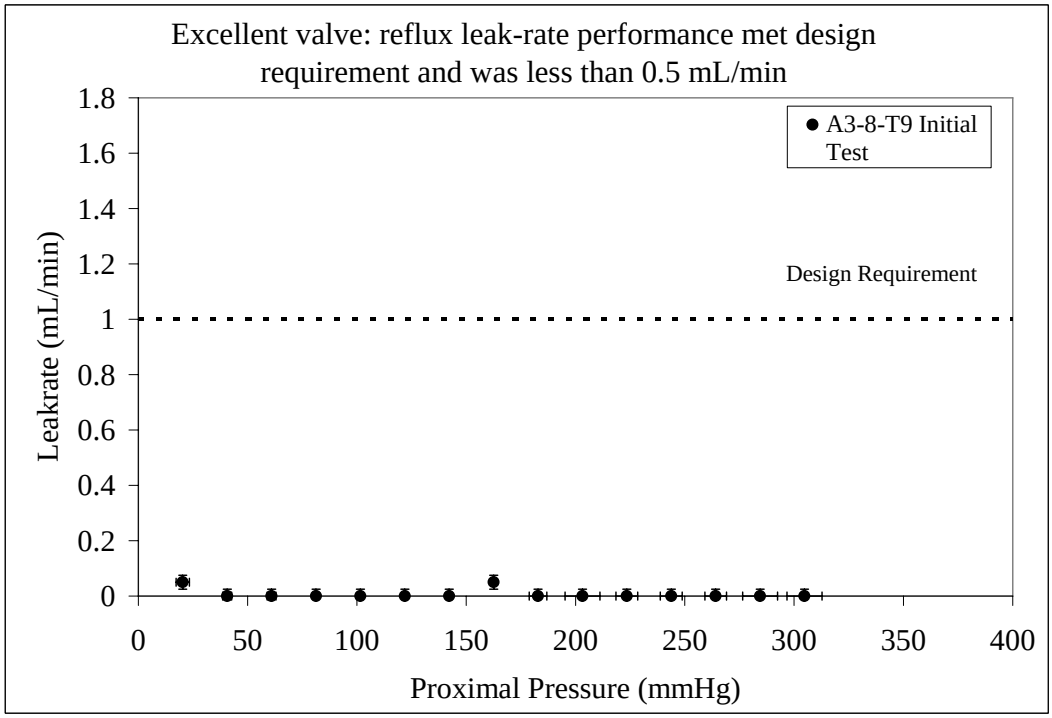


Figure 53: Competency assessment of 3 cycle valve (A3-8-T9)

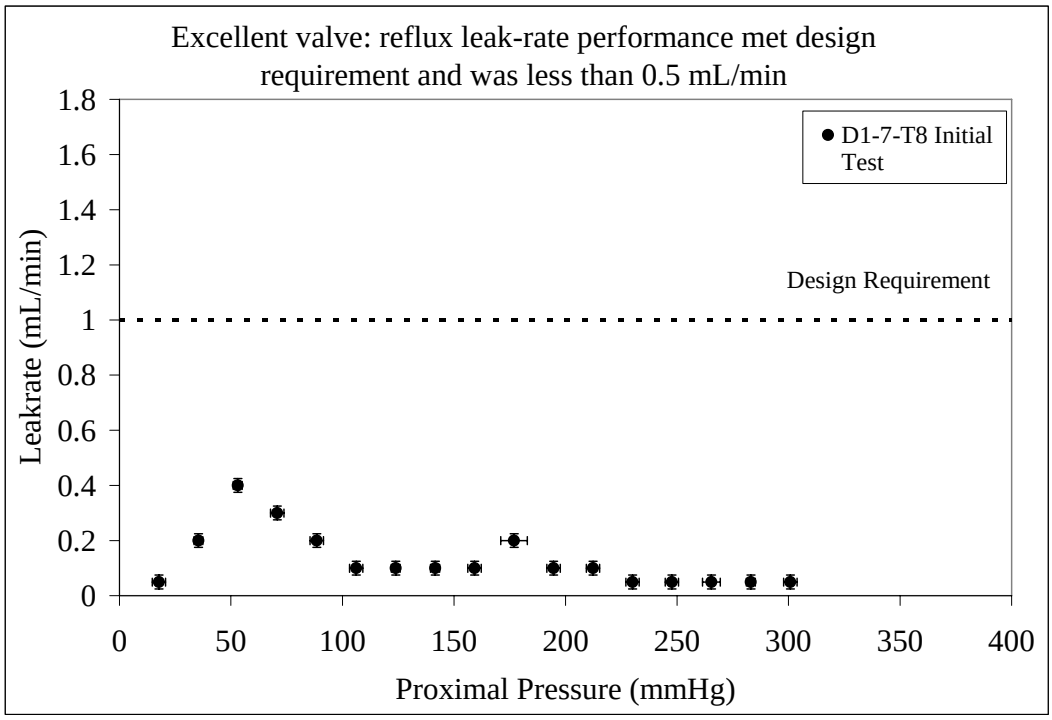


Figure 54: Competency assessment of 3 cycle valve (D1-7-T8)

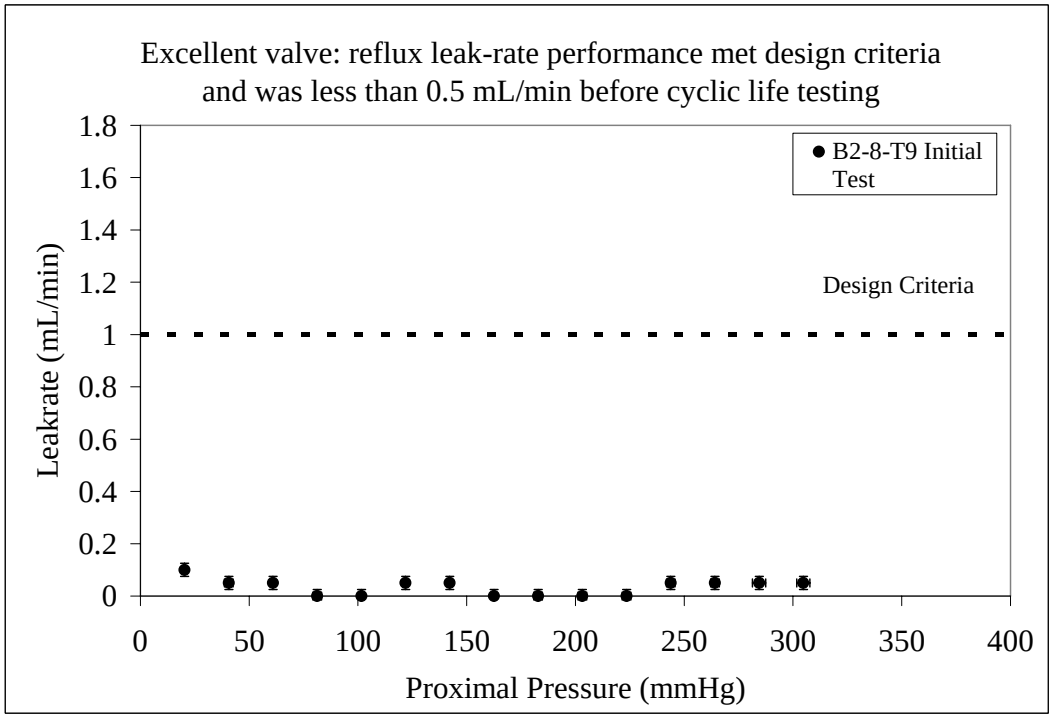


Figure 55: Competency assessment of 3 cycle valve (B2-8-T9)

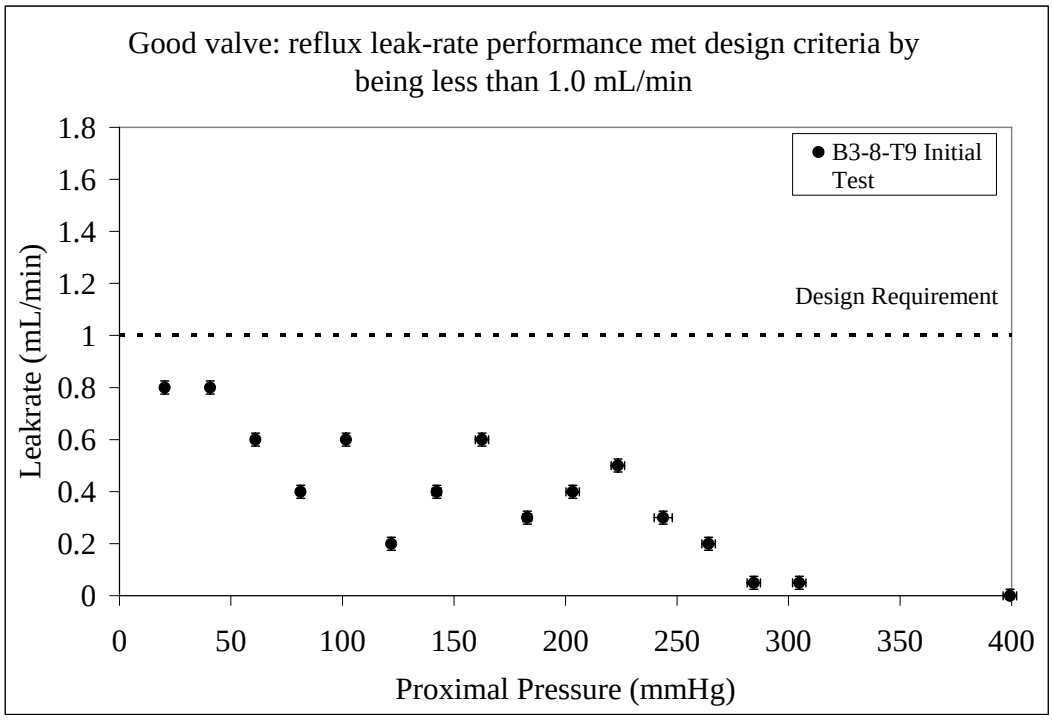


Figure 56: Competency assessment of 3 cycle valve (B3-8-T9)

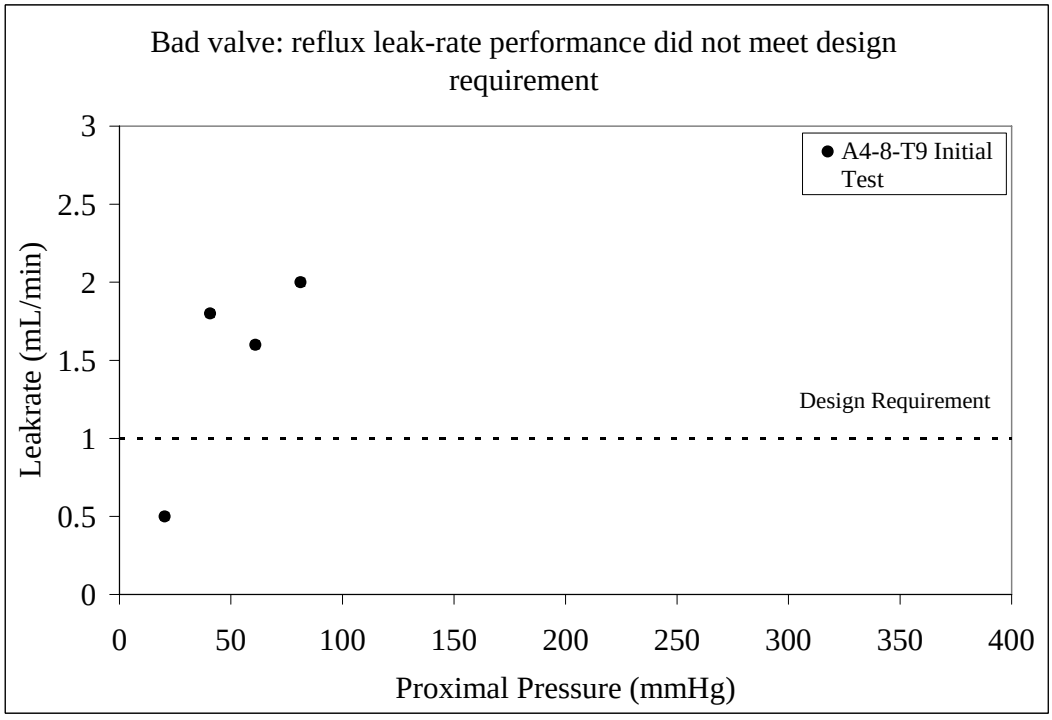


Figure 57: Competency assessment of 3 cycle valve (A4-8-T9)

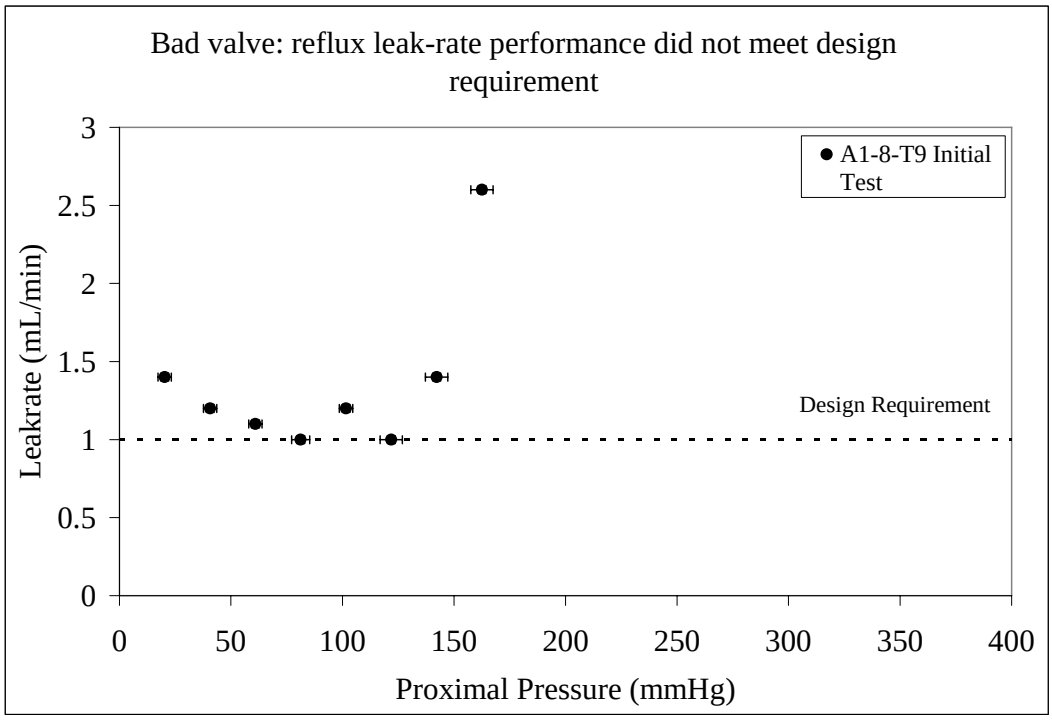


Figure 58: Competency assessment of 3 cycle valve (A1-8-T9)

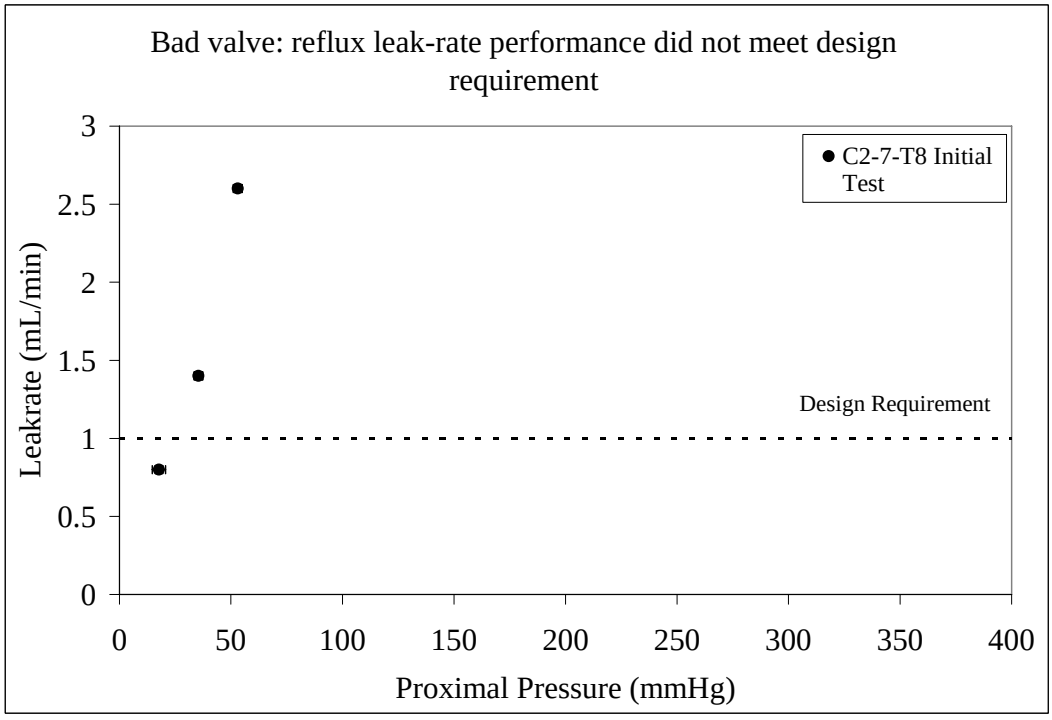


Figure 59: Competency assessment of 3 cycle valve (C2-7-T8)

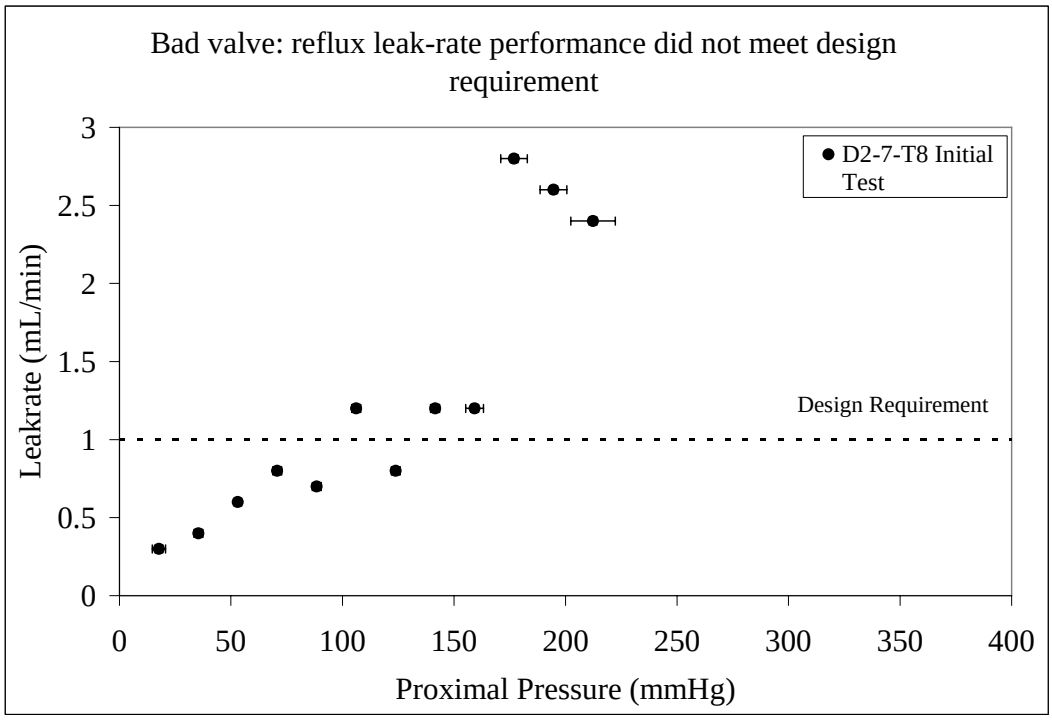


Figure 60: Competency assessment of 3 cycle valve (D2-7-T8)

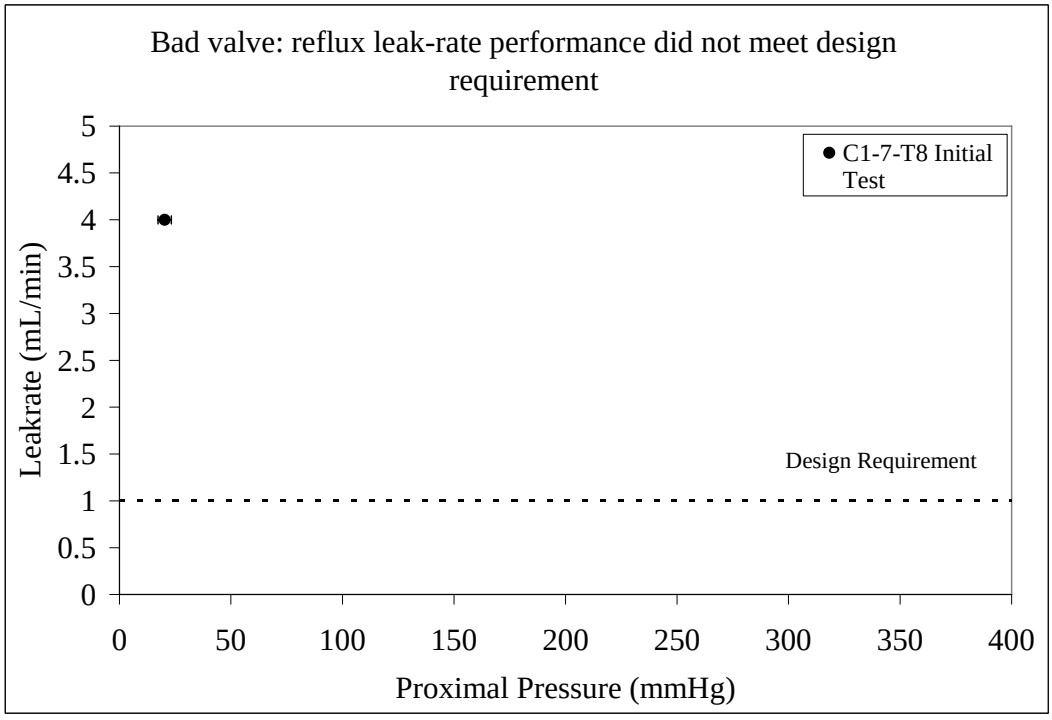


Figure 61: Competency assessment of 3 cycle valve (C1-7-T8)

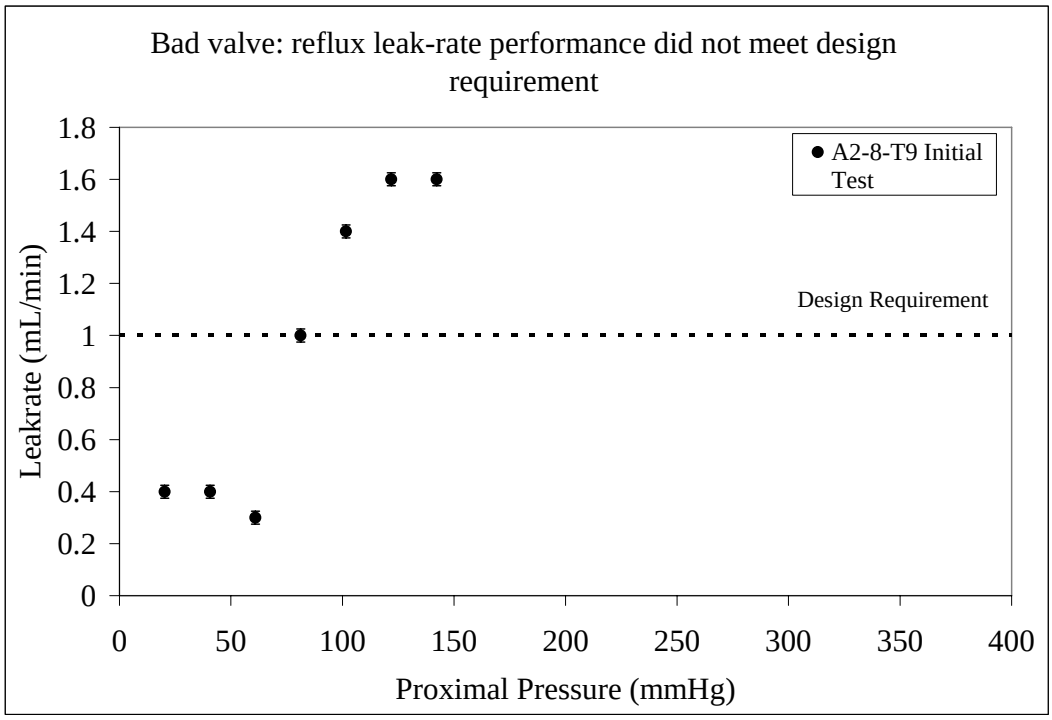


Figure 62: Competency assessment of 3 cycle valve (A2-8-T9)

TEST B (REFLUX LEAKAGE) RESULTS FOR 5 FREEZE-THAW CYCLE VALVE

Figures 63 - 74 depict the reflux leak-rate performance during proximal pressure testing for individual valves fabricated using 5 freeze-thaw cycles. Leak-rates were recorded from 0 mmHg to 300 mmHg. In cases where leak-rate exceeded 2.0 mL/min, the test was terminated, and leak-rate data was not acquired at higher pressures. The design requirement for proximal pressure performance was that the valve does not exceed 1.0 mL/min of reflux leakage at any applied proximal pressure from 0 to 300 mmHg. Excellent valves were valves having leak-rates equivalent or less than 0.5 mL/min. Good valves were valves having leak-rates that met the design criteria. Bad valves had leakage greater than the design criteria.

Table 20: Description of categorizing valve competency

Valve Categorization	Description of criteria
Excellent	Leak-rate $\leq$ 0.5 mL/min
Good	0.5 mL/min < Leak-rate $\leq$ 1.0 mL/min
Bad	Leak-rate > 1.0 mL/min

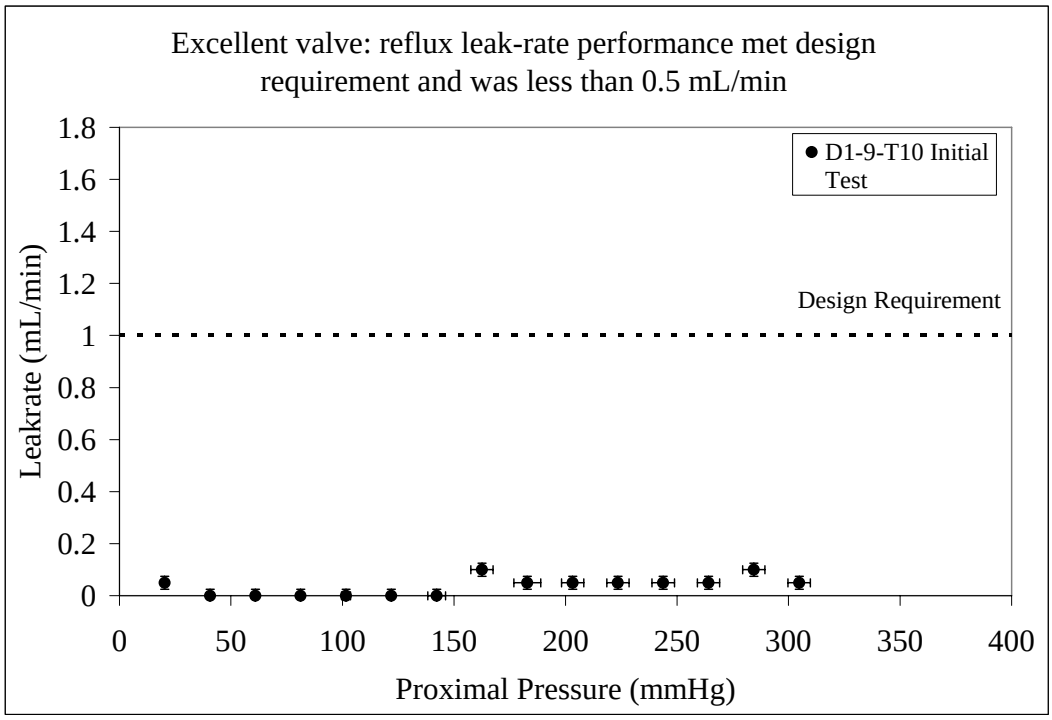


Figure 63: Competency assessment of 5 cycle valve (D1-9-T10)

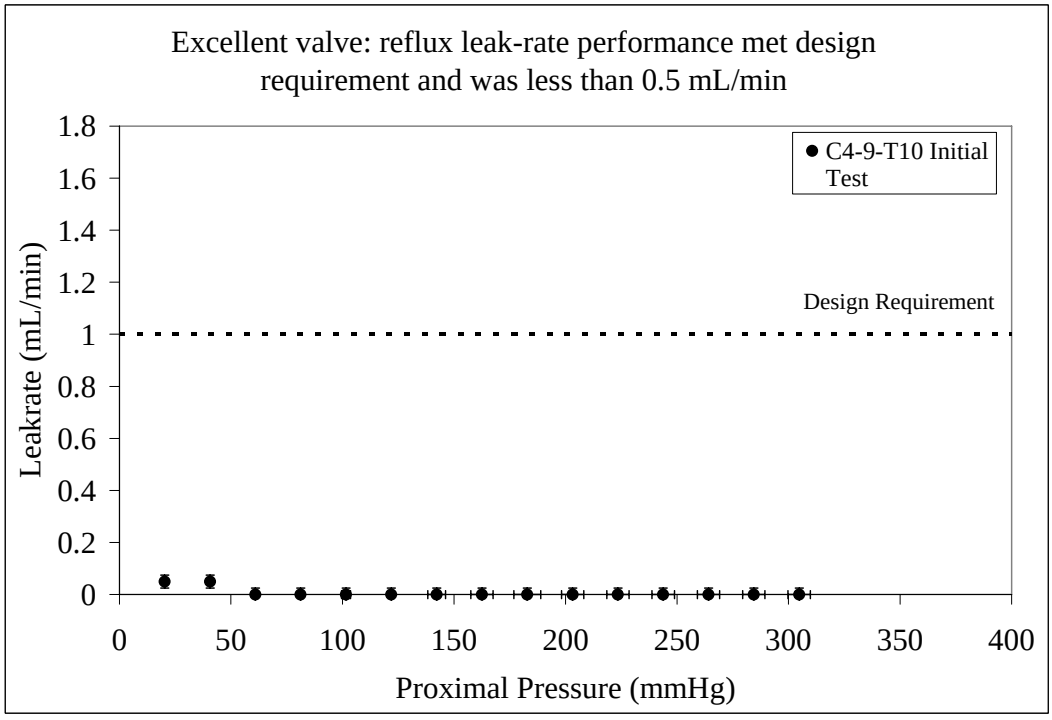


Figure 64: Competency assessment of 5 cycle valve (C4-9-T10)

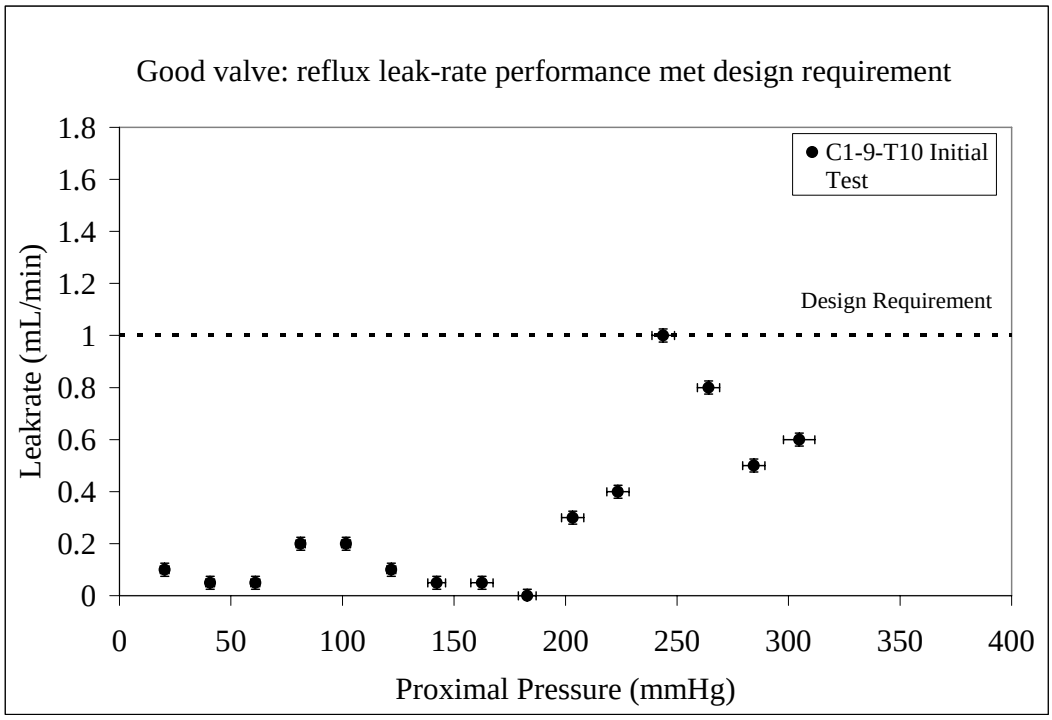


Figure 65: Competency assessment of 5 cycle valve (C1-9-T10)

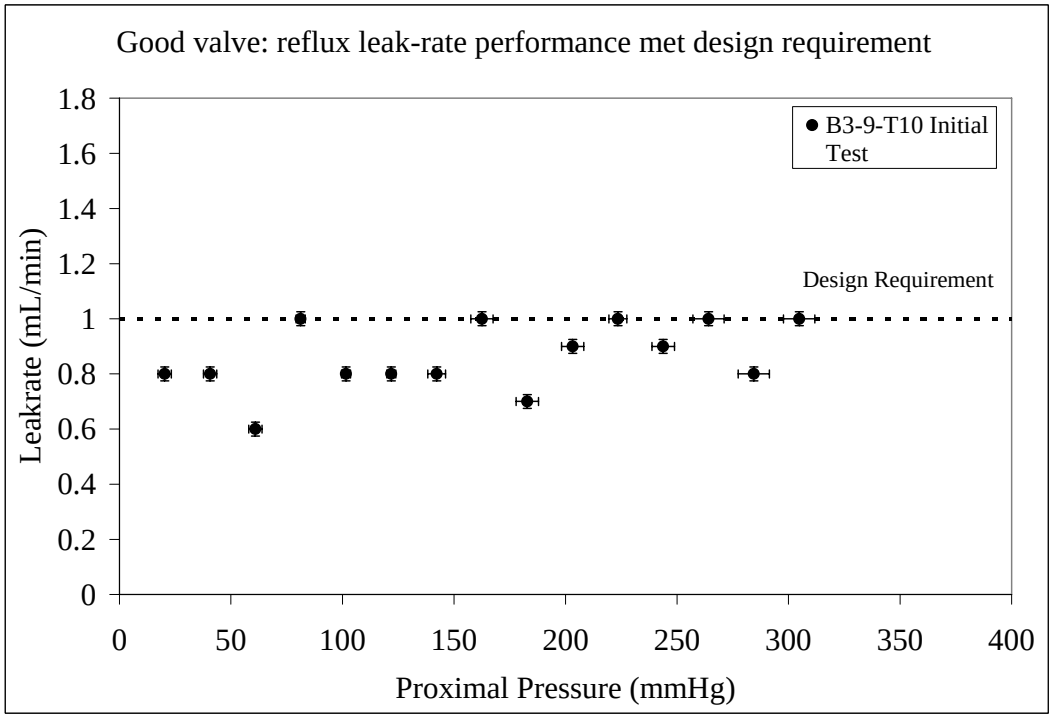


Figure 66: Competency assessment of 5 cycle valve (B3-9-T10)

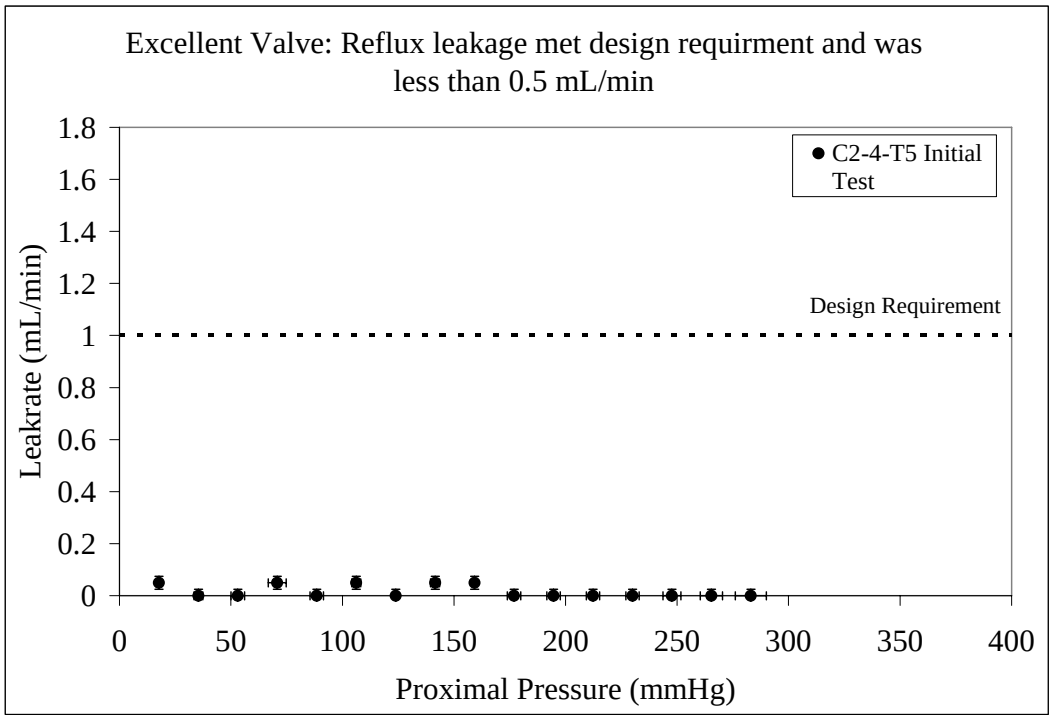


Figure 67: Competency assessment of 5 cycle valve (C2-4-T5)

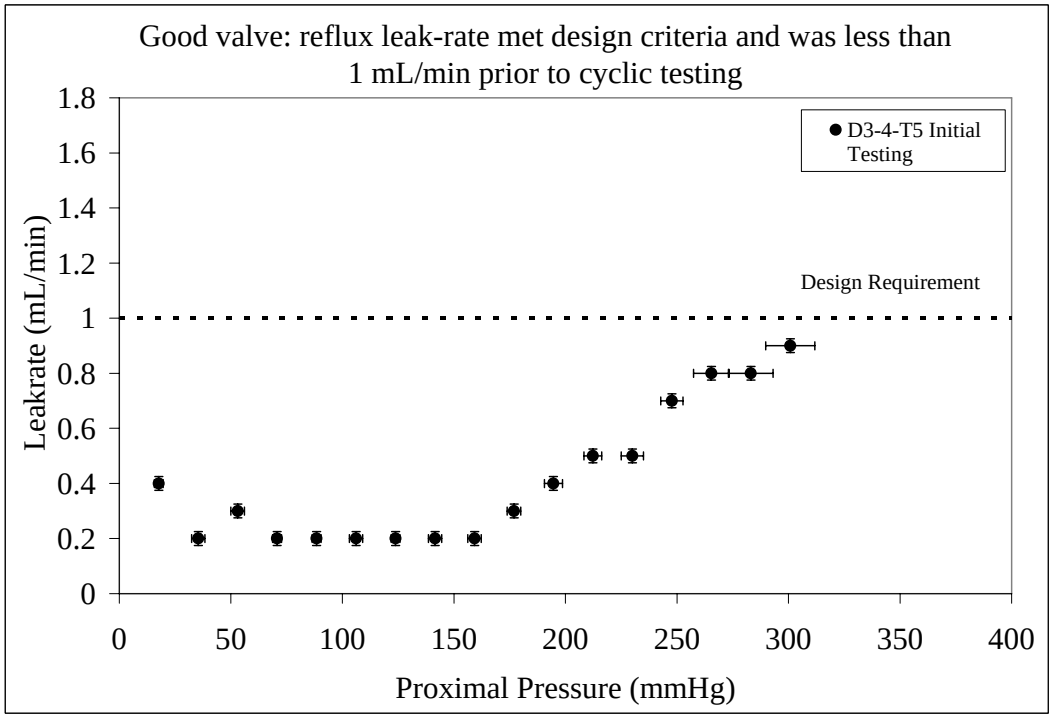


Figure 68: Competency assessment of 5 cycle valve (D3-4-T5)

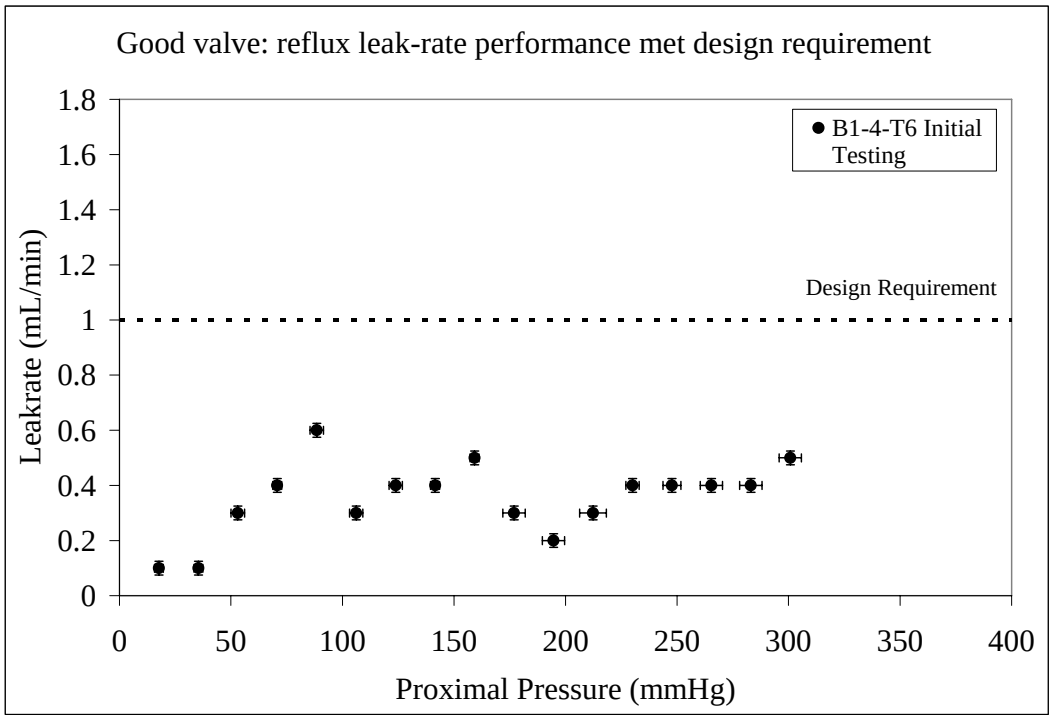


Figure 69: Competency assessment of 5 cycle valve (B1-4-T6)

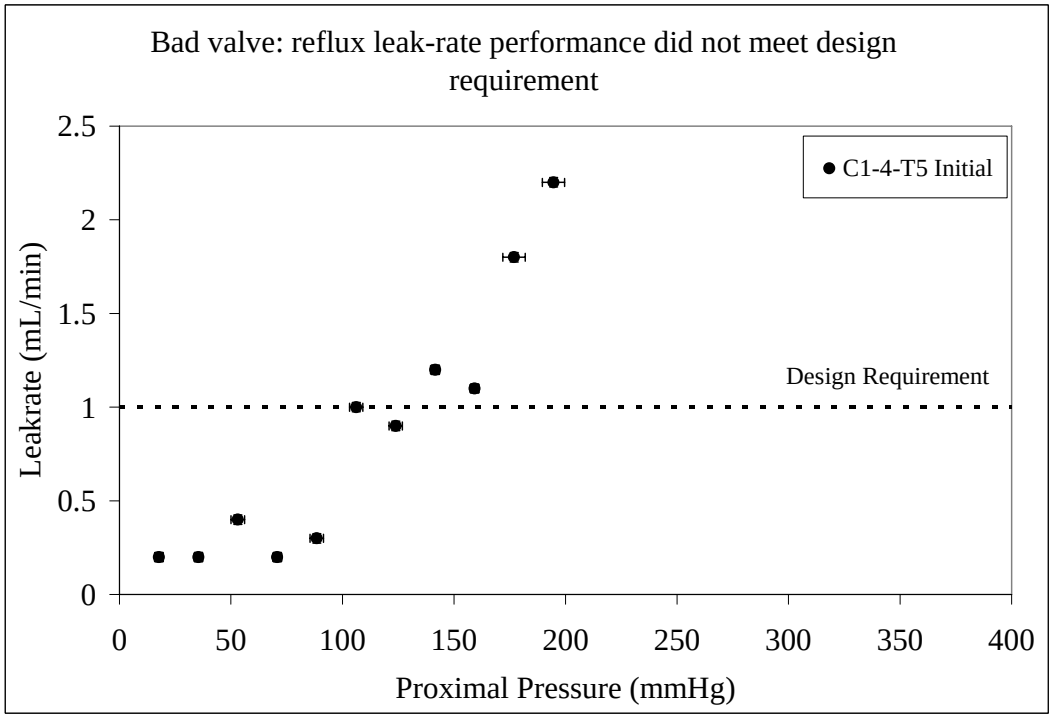


Figure 70: Competency assessment of 5 cycle valve (C1-4-T5)

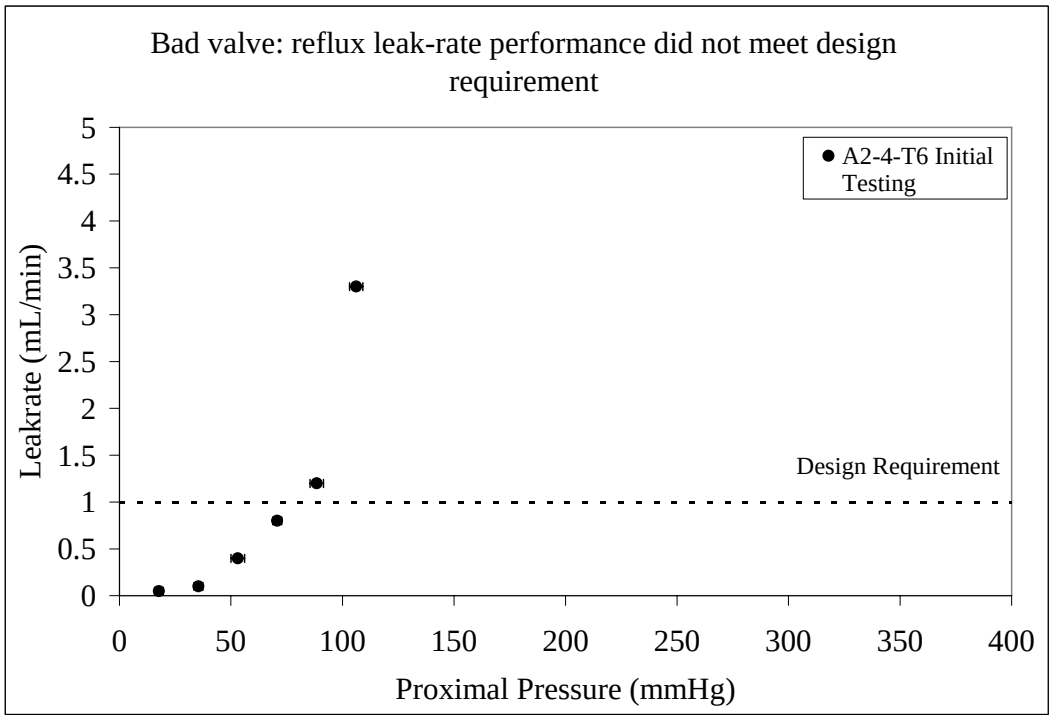


Figure 71: Competency assessment of 5 cycle valve (A2-4-T6)

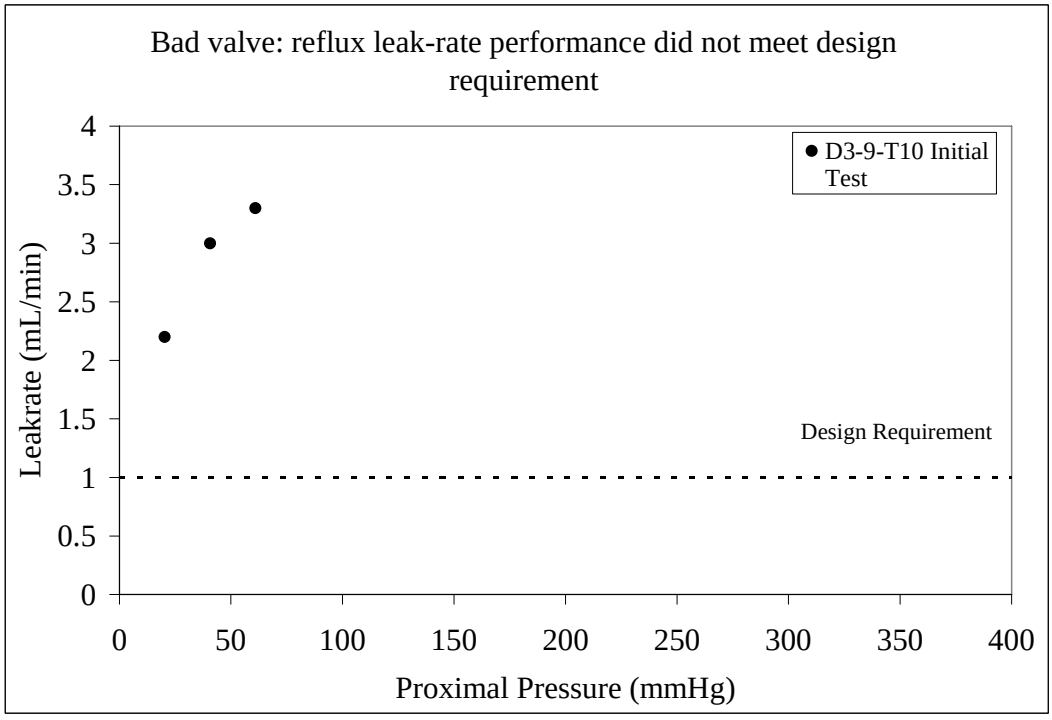


Figure 72: Competency assessment of 5 cycle valve (D3-9-T10)

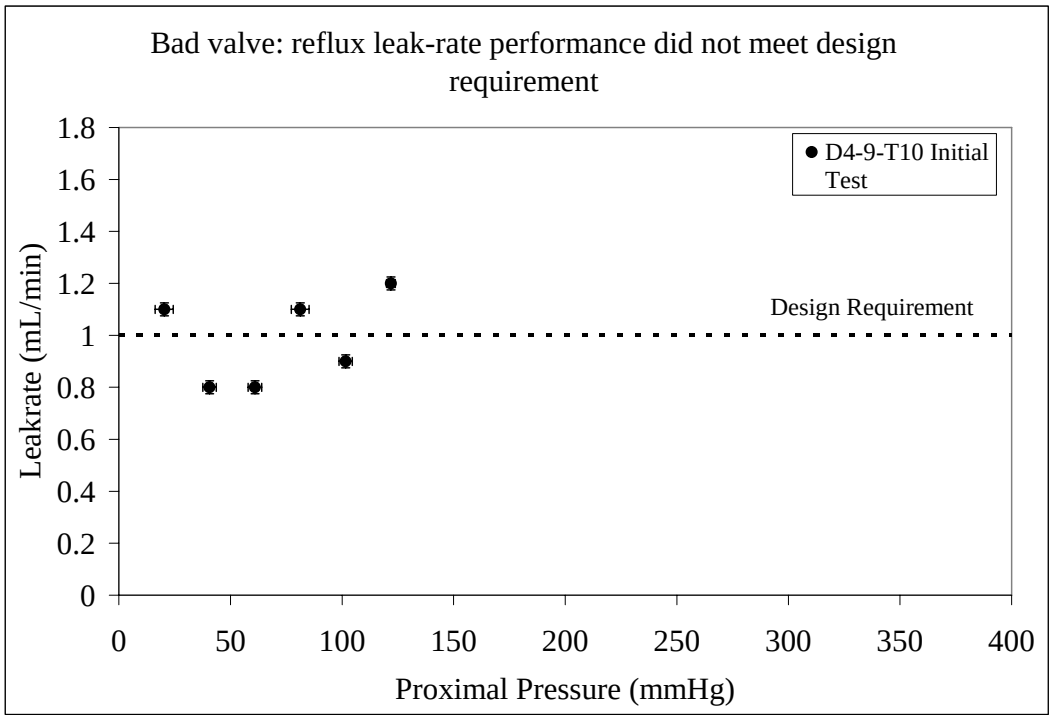


Figure 73: Competency assessment of 5 cycle valve (D4-9-T10)

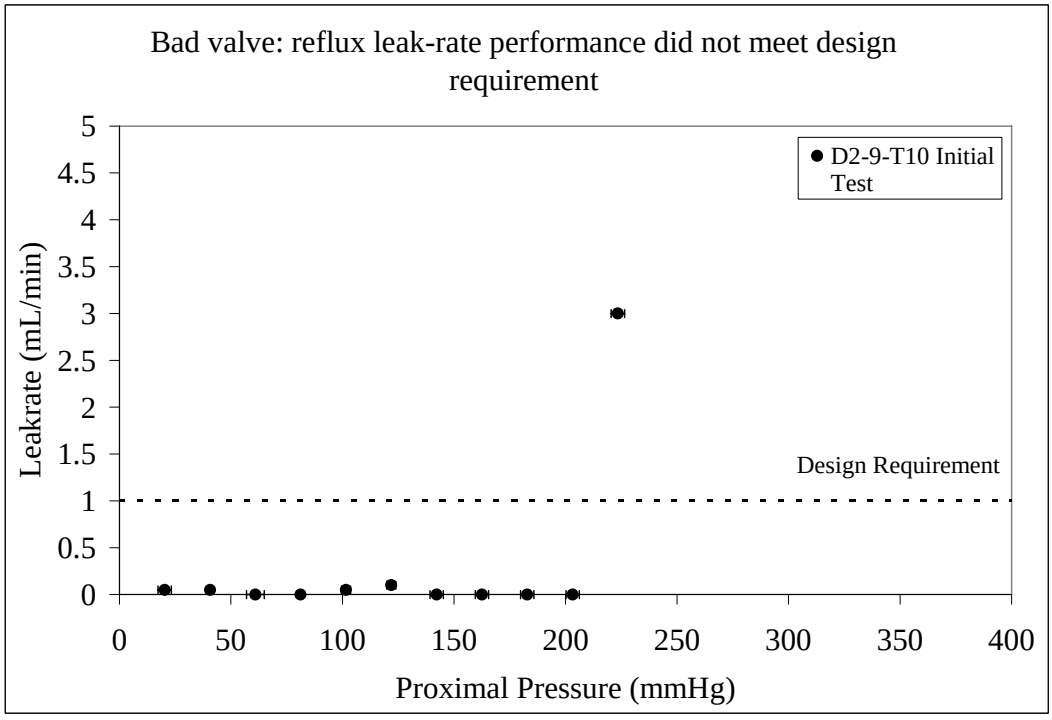


Figure 74: Competency assessment of 5 cycle valve (D2-9-T10)

TEST D (CYCLIC LIFE FUNCTIONALITY) RESULTS FOR 3 FREEZE-THAW CYCLE VALVE

Table 21 and Figure 75 depict the opening pressure of a 3 freeze-thaw cycle valve throughout cyclic life testing. Figures 76 – 82 depict the competency of the valve throughout cyclic life testing.

Table 21: Opening pressure throughout cyclic life testing for a 3 freeze-thaw cycle valve (specimen B2-8-T9)

Approximate # of open-close cycles	Initial opening pressure (mmHg)	Opening pressure after reflux testing (mmHg)
0 (Initial test)	3.3 ± 0.7	7.3 ± 1.0
68,000	2.6 ± 0.7	4.7 ± 1.0
136,000	3.5 ± 0.5	4.3 ± 0.7
193,000	3.5 ± 0.7	5.3 ± 0.7
253,000	3.7 ± 0.7	5.3 ± 0.7
385,000	4.3 ± 0.7	3.9 ± 0.7
508,000	3.3 ± 0.7	3.3 ± 0.7

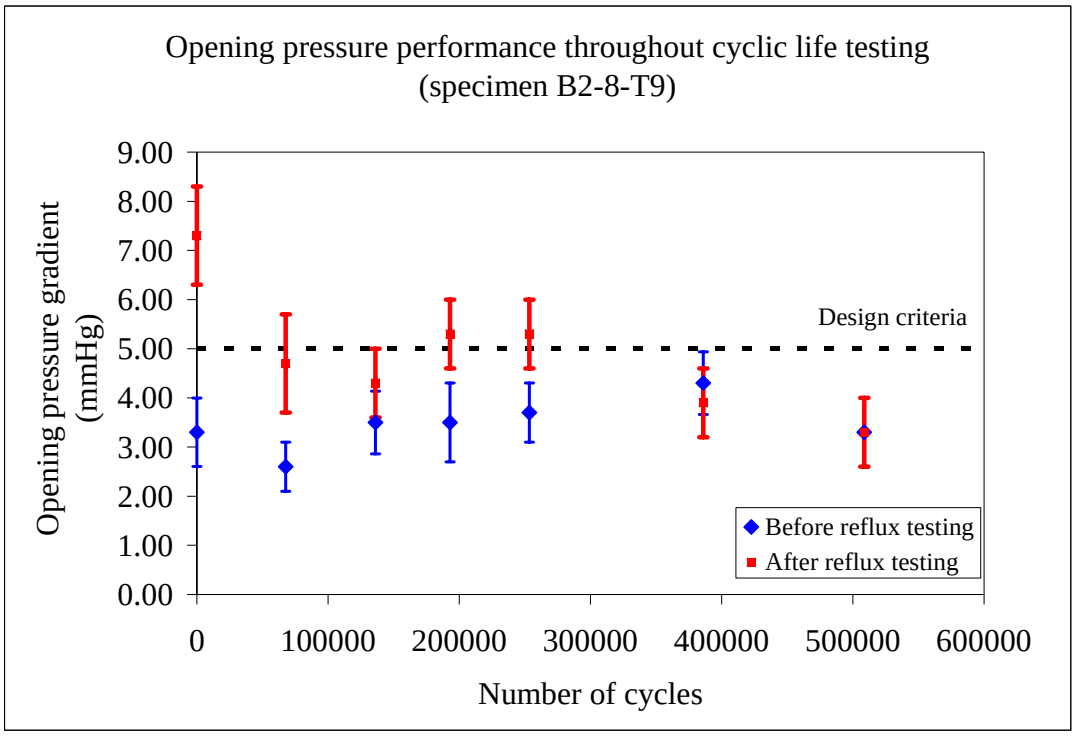


Figure 75: Valve opening pressures for a 3 freeze-thaw cycle valve measured before reflux testing met design criteria throughout cyclic life testing. High reflux pressure (300 mmHg) sustained for 30 seconds increased the valve's opening pressure early during the valve's cyclic life testing.

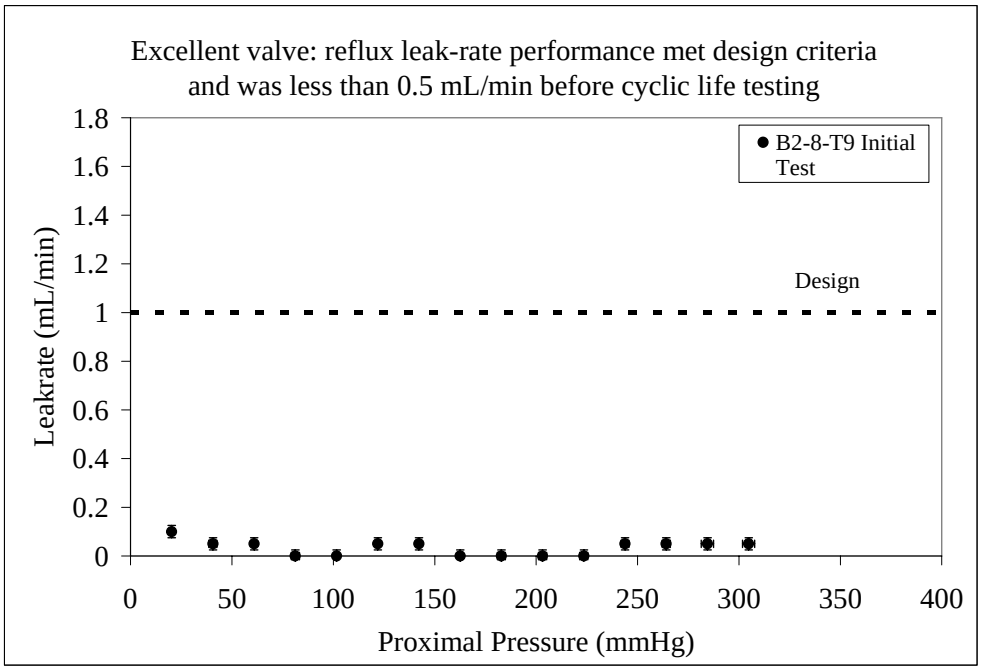


Figure 76: Prior to cyclic life testing, a 3 freeze-thaw cycle valve met a key design criterion of having less than 1 mL/min of leak-rate (specimen B2-8-T9).

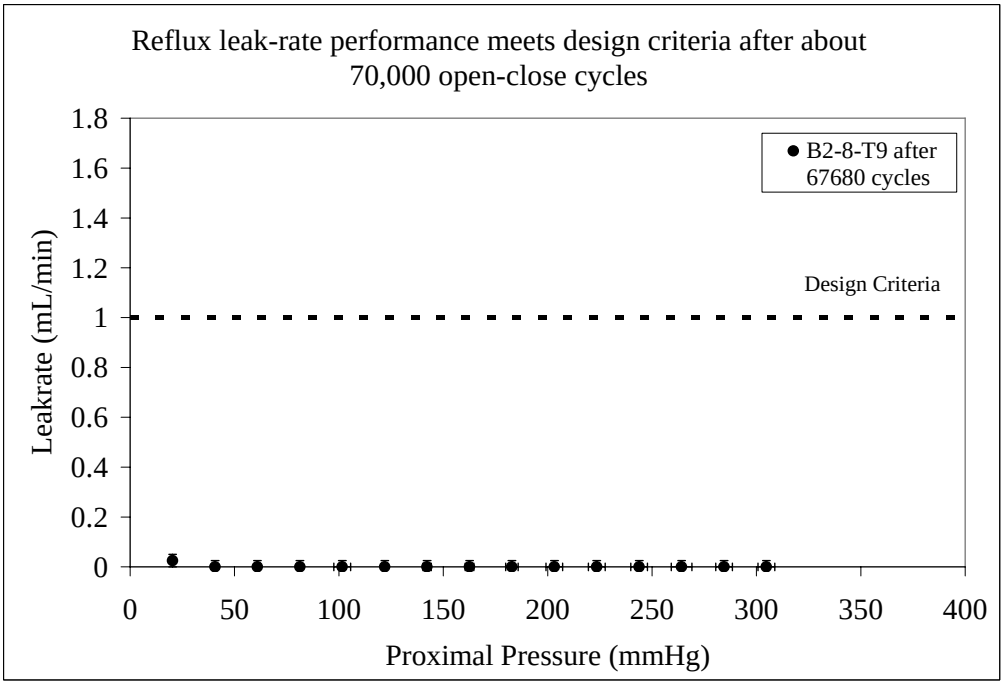


Figure 77: After approximately 70,000 open-close cycles, a 3 freeze-thaw cycle valve met a key design criterion of having less than 1 mL/min of leak-rate (specimen B2-8-T9).

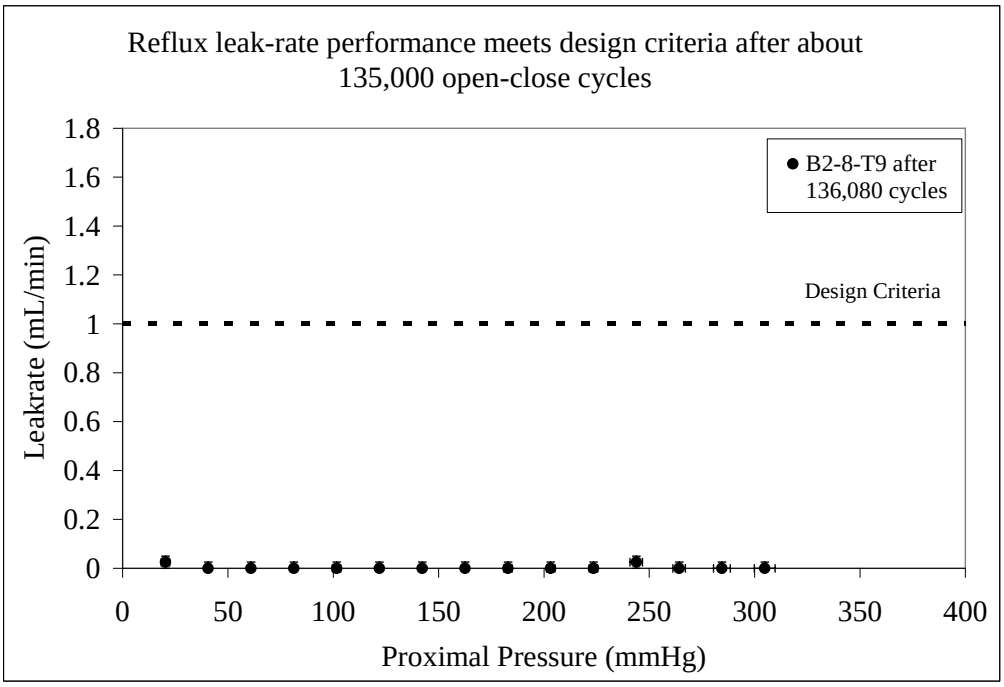


Figure 78: After approximately 135,000 open-close cycles, a 3 freeze-thaw cycle valve met a key design criterion of having less than 1 mL/min of leak-rate (specimen B2-8-T9).

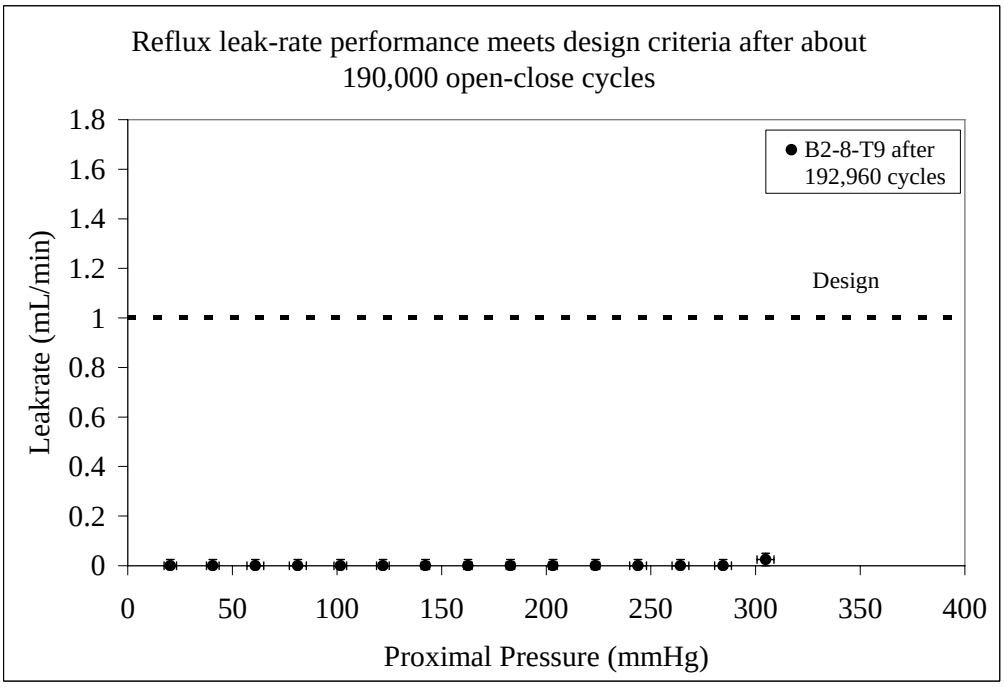


Figure 79: After approximately 190,000 open-close cycles, a 3 freeze-thaw cycle valve met a key design criterion of having less than 1 mL/min of leak-rate (specimen B2-8-T9).

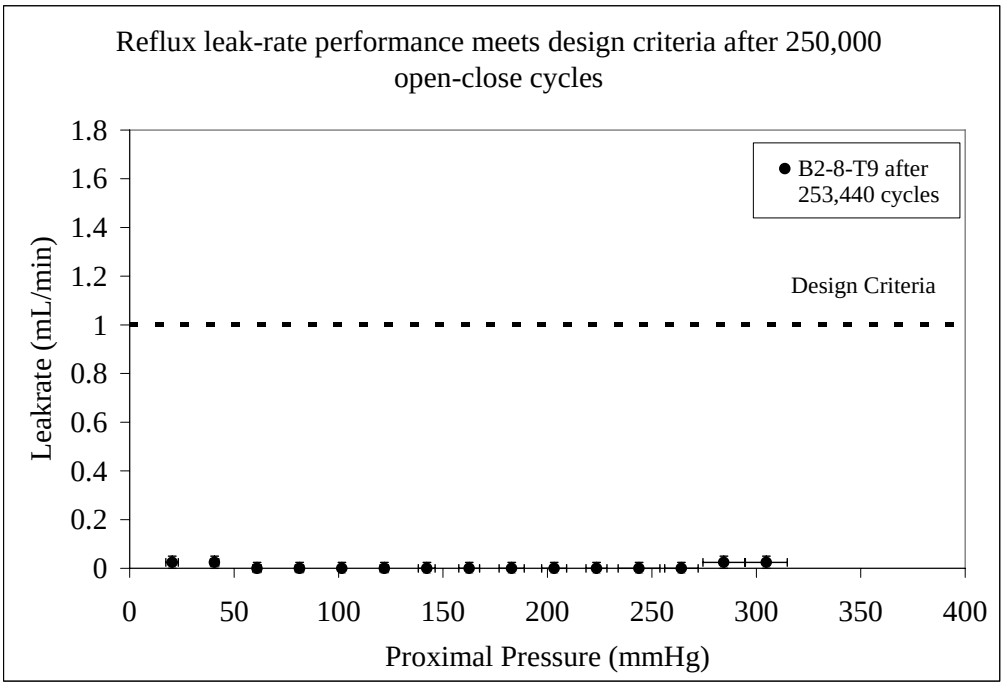


Figure 80: After approximately 250,000 open-close cycles, a 3 freeze-thaw cycle valve met a key design criterion of having less than 1 mL/min of leak-rate (specimen B2-8-T9).

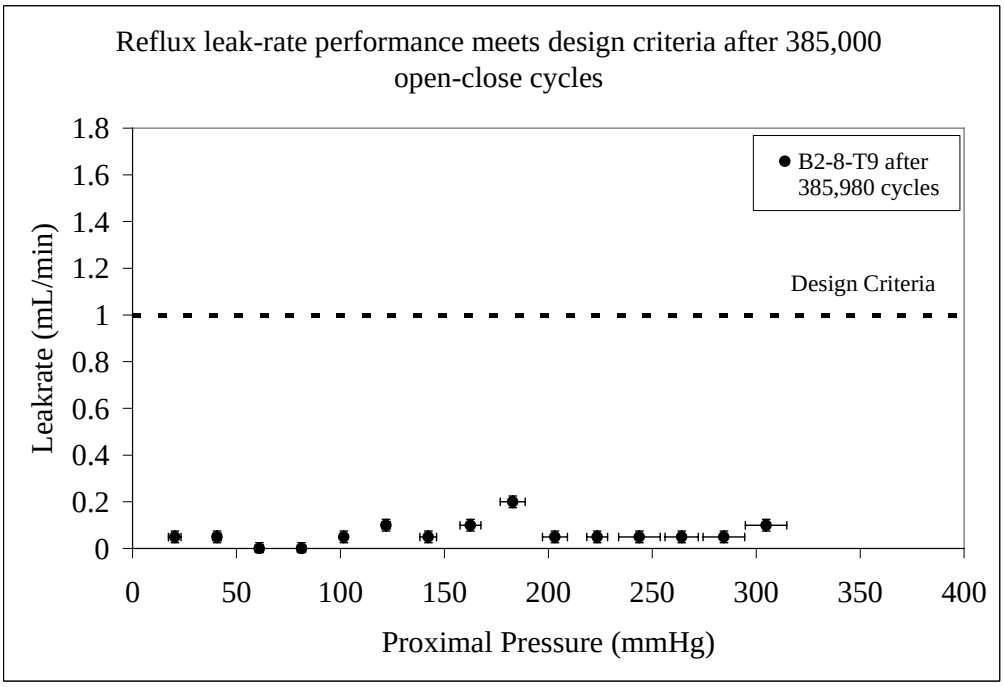


Figure 81: After approximately 385,000 open-close cycles, a 3 freeze-thaw cycle valve met a key design criterion of having less than 1 mL/min of leak-rate (specimen B2-8-T9).

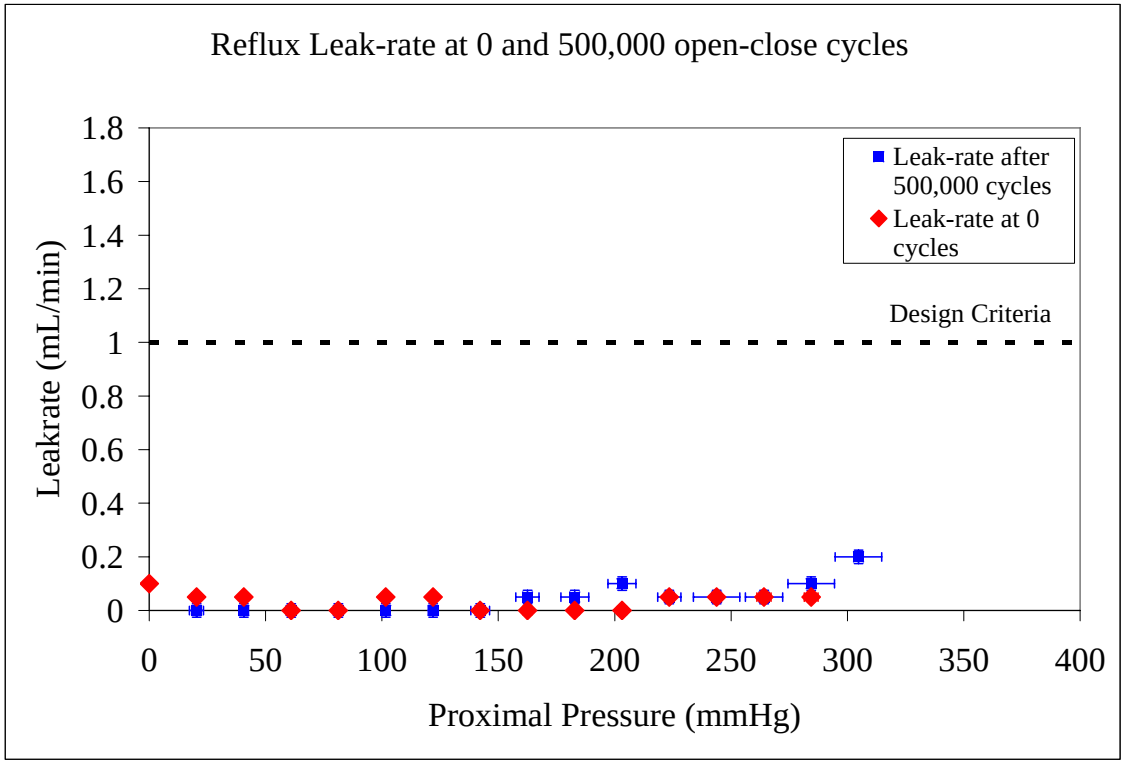


Figure 82: After 500,000 open-close cycles, a 3 freeze-thaw cycle valve met a key design criterion of having less than 1 mL/min of leak-rate (specimen B2-8-T9). An "excellent" valve like B2-8-T9 (3 freeze-thaw cycles) maintained excellent leak-rate characteristics even after 500,000 open-close cycles. This excellent performance can be attributed to the valve being in excellent condition prior to any cyclic testing. Cyclic testing was terminated after this evaluation of the valve because test equipment began to break. The test was not terminated because of the valve.

TEST D (CYCLIC LIFE FUNCTIONALITY) RESULTS FOR 5 FREEZE-THAW CYCLE VALVE

Table 22 and Figure 83 depict the opening pressure of a 5 freeze-thaw cycle throughout cyclic life testing. Figures 84 – 90 depict the competency of the valve throughout cyclic life testing.

Table 22: Opening pressure throughout cyclic life testing (D3-4-T5) for a 5 freeze-thaw cycle valve

Approximate # of open-close cycles	Initial opening pressure (mmHg)	Opening pressure after reflux testing (mmHg)
0 (Initial test)	3.9 ± 0.7	NA
27,000	2.7 ± 0.5	5.3 ± 1.2
62,000	2.5 ± 0.7	5.0 ± 0.7
124,000	2.7 ± 0.8	3.9 ± 0.7
182,000	2.8 ± 0.6	4.0 ± 0.7
244,000	2.8 ± 0.6	6.0 ± 0.9
295,000*	2.0 ± 0.6	NA

*Test terminated after 295,000 cycles

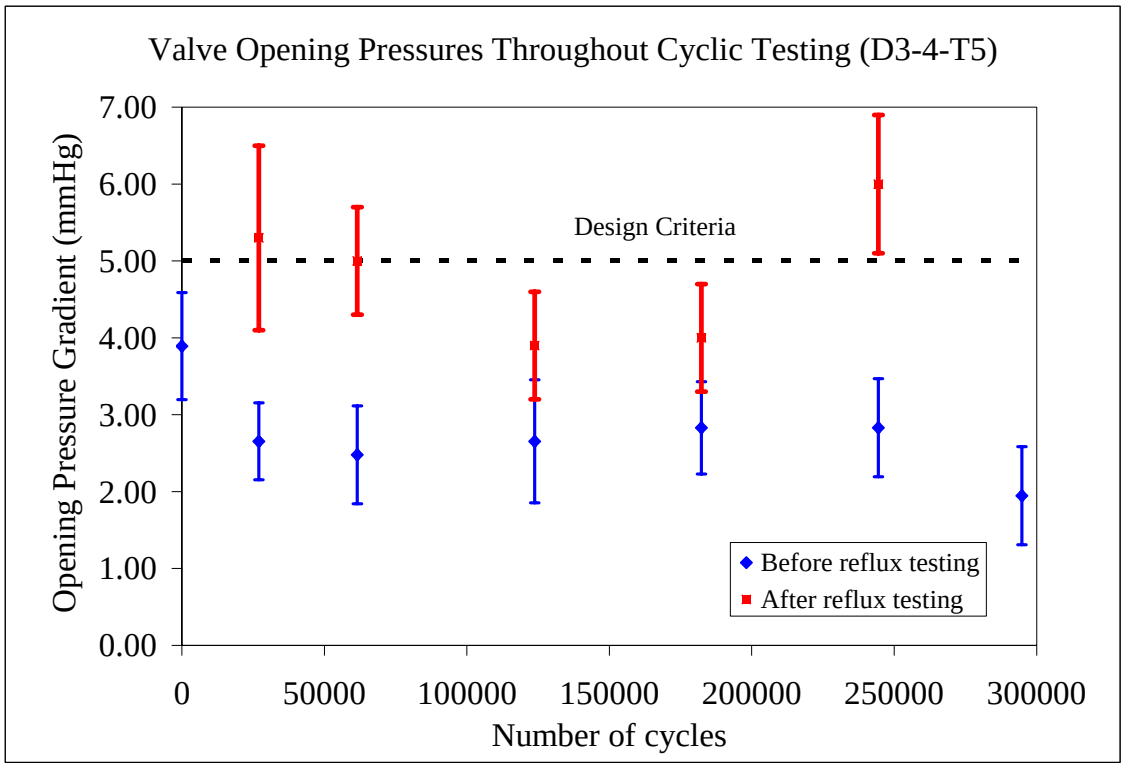


Figure 83: Valve opening pressures for a 5 freeze-thaw cycle valve measured before reflux testing met design criteria throughout cyclic life testing. High reflux pressure (300 mmHg) sustained for 30 seconds increased the valve's opening pressure.

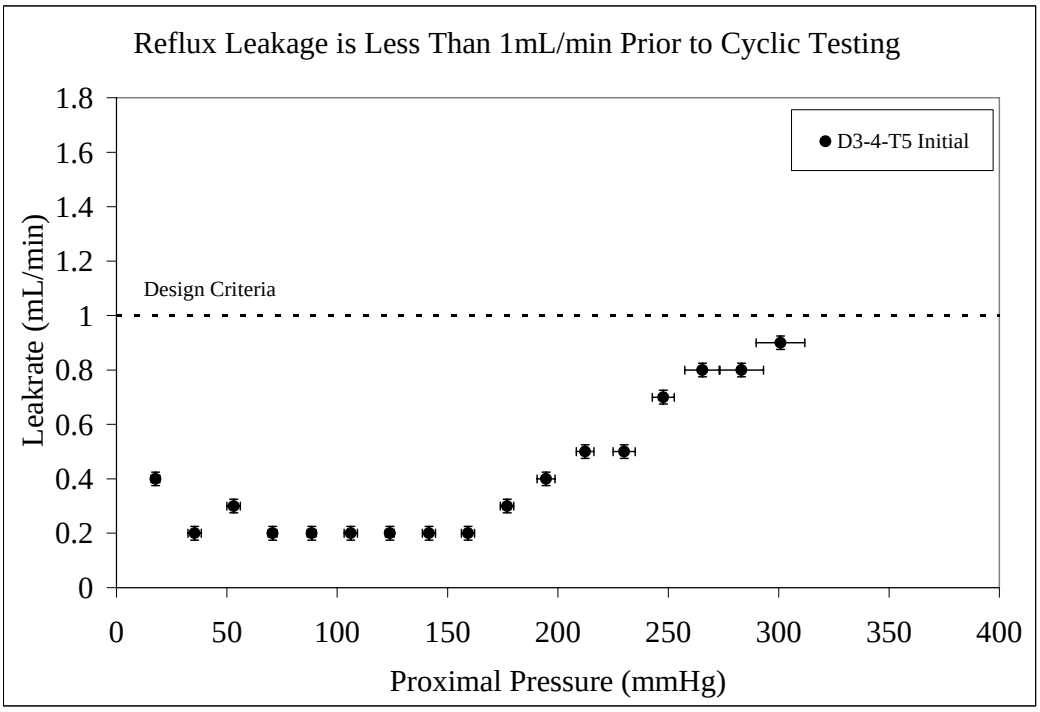


Figure 84: Prior to any cyclic testing, a 5 freeze-thaw cycle valve met a key design criterion of having less than 1 mL/min of leak-rate (specimen D3-4-T5).

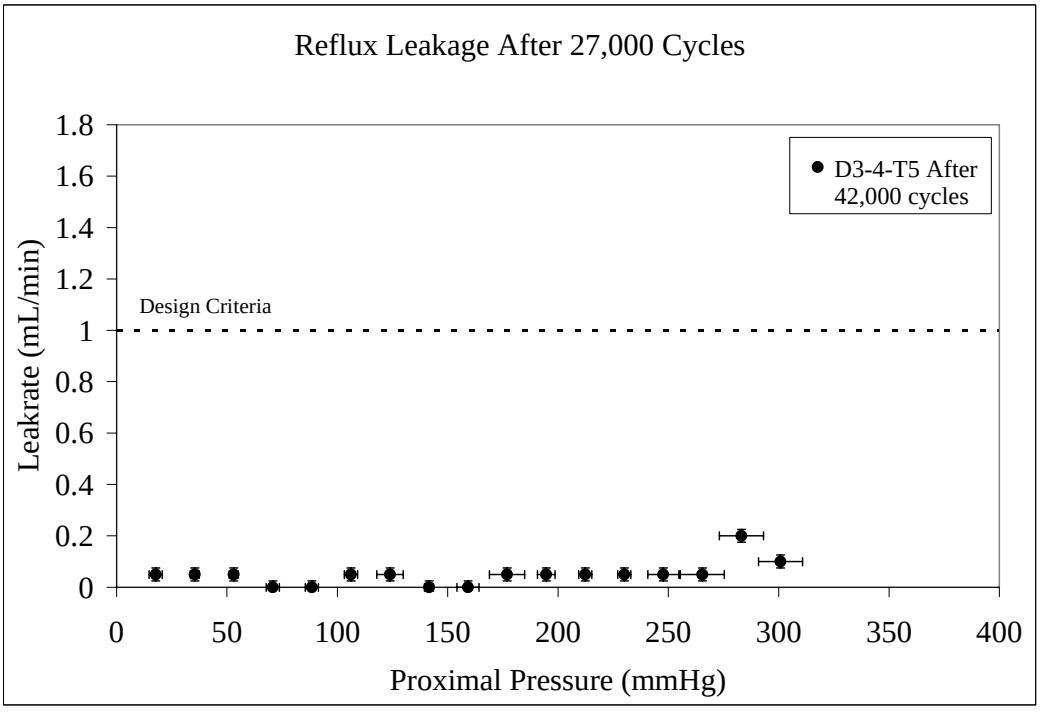


Figure 85: After 27,000 open-close cycles, a 5 freeze-thaw cycle valve met a key design criterion of having less than 1 mL/min of leak-rate (specimen D3-4-T5).

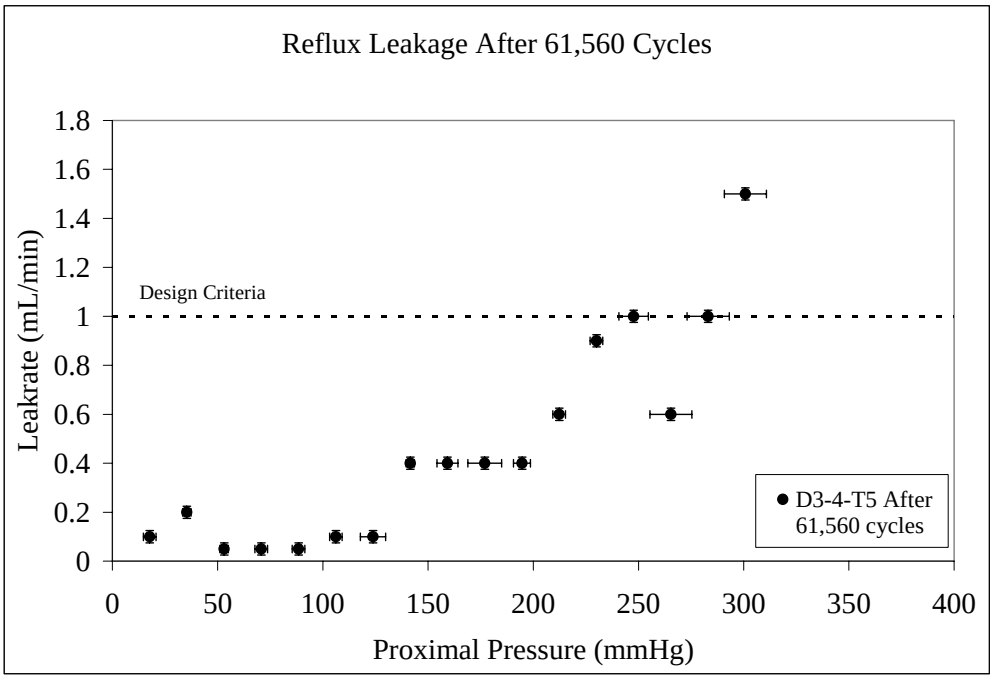


Figure 86: After nearly 62,000 open-close cycles, a 5 freeze-thaw cycle valve met the leak-rate criterion for proximal pressures less than 250 mmHg (specimen D3-4-T5).

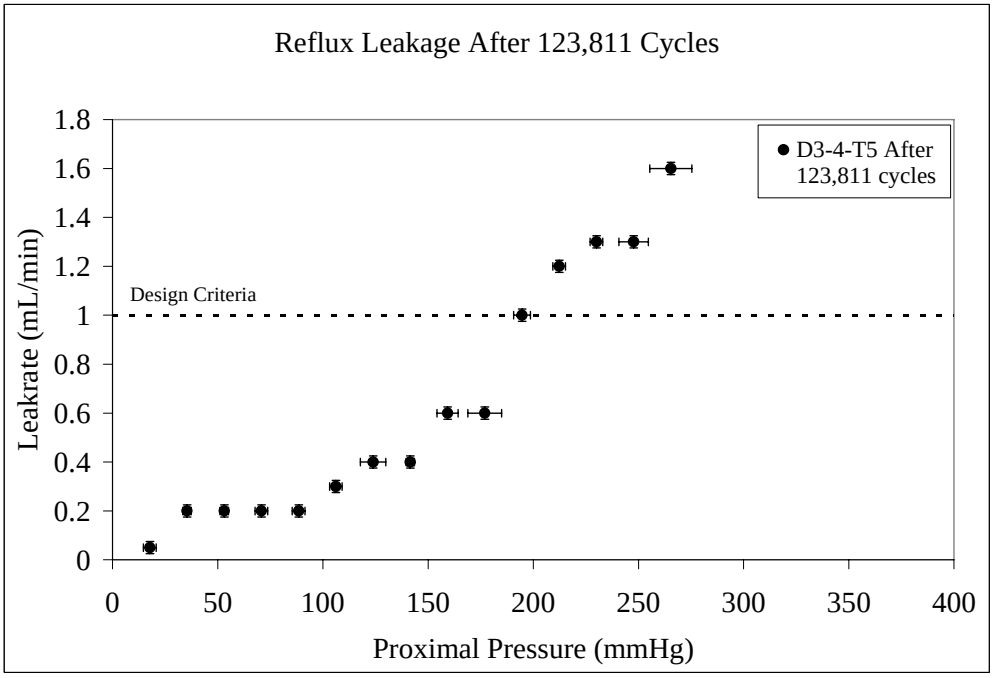


Figure 87: After nearly 124,000 open-close cycles, a 5 freeze-thaw cycle valve met the leak-rate criterion for proximal pressures less than 200 mmHg (specimen D3-4-T5).

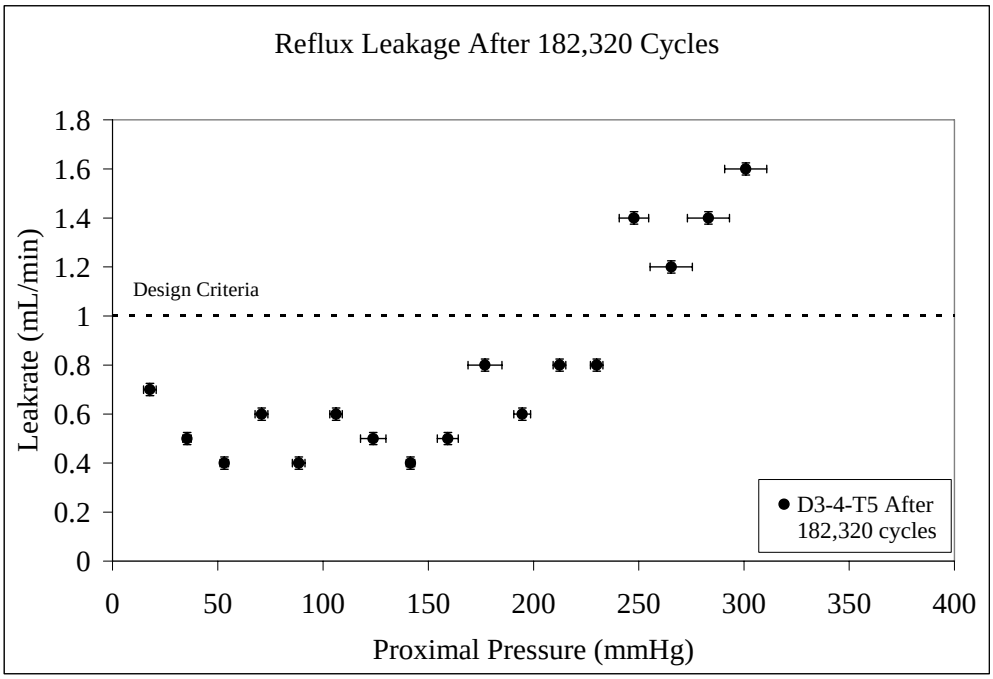


Figure 88: After approximately 182,000 open-close cycles, a 5 freeze-thaw cycle valve met the leak-rate criterion for proximal pressures less than 200 mmHg (specimen D3-4-T5).

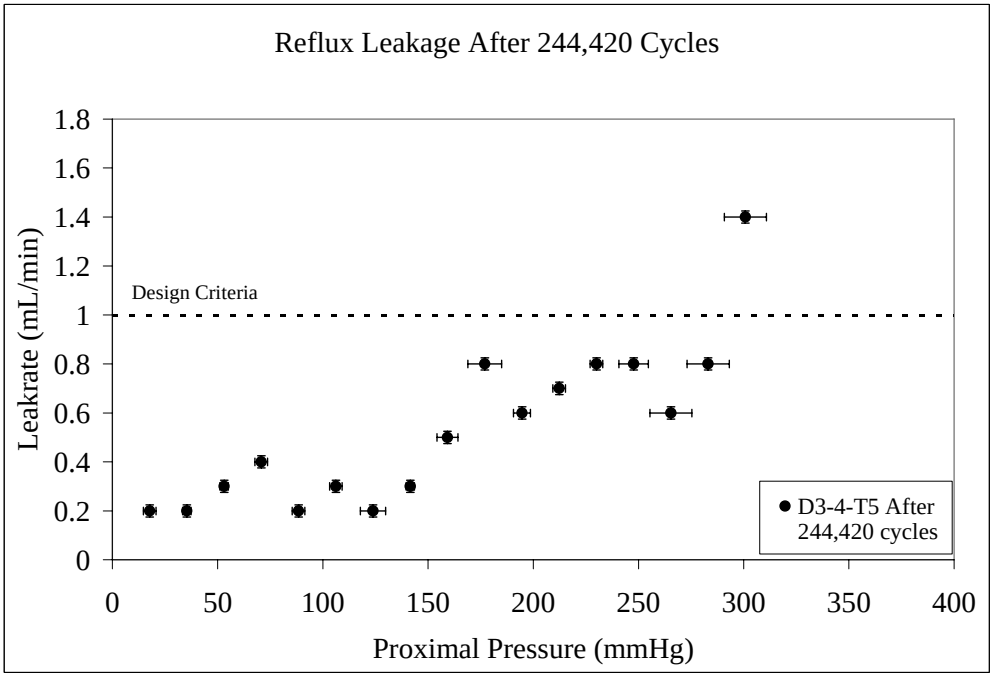


Figure 89: After approximately 244,000 open-close cycles, a 5 freeze-thaw cycle valve met the leak-rate criterion for proximal pressures less than 280 mmHg (specimen D3-4-T5).

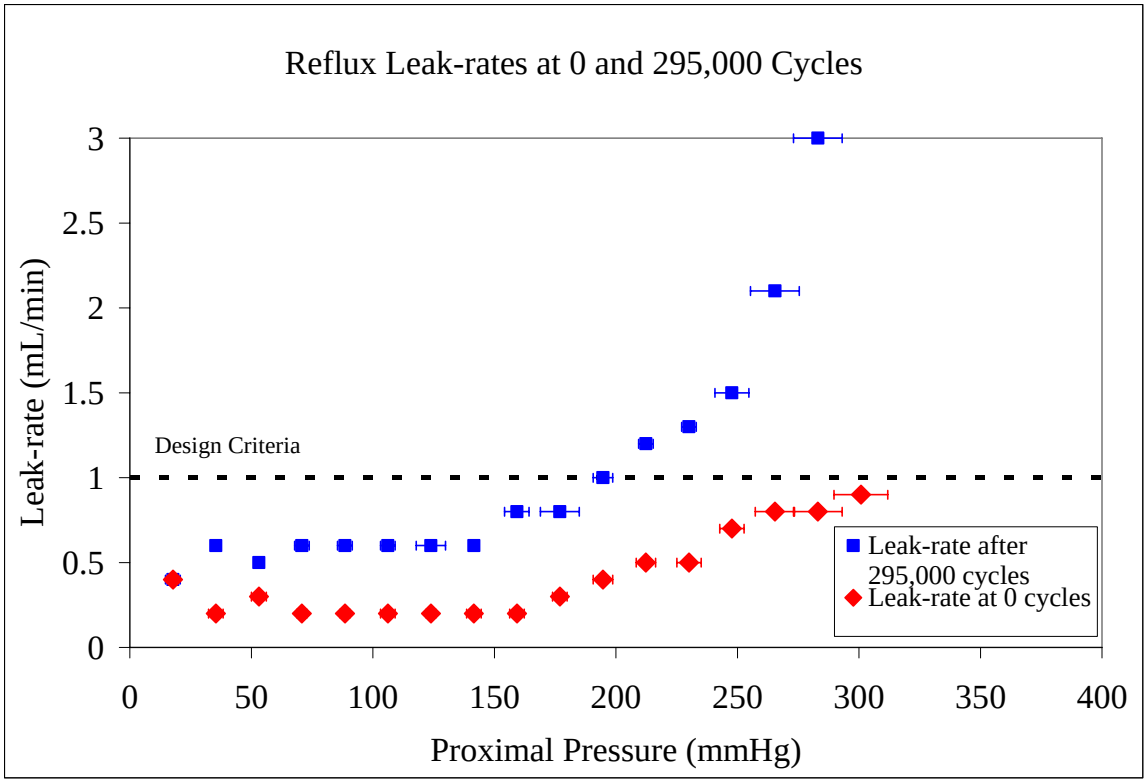


Figure 90: After approximately 295,000 open-close cycles, a 5 freeze-thaw cycle valve met the leak-rate criterion for proximal pressures less than 200 mmHg (specimen D3-4-T5).

The degradation in reflux performance is most likely due to initial deformities in the leaflet sealing area. At 0 cycles, this valve was only "good" and not "excellent," allowing leak-rates between 0.5 and 1.0 mL/min at proximal pressures greater than 200 mmHg. Cracks or leaflet surface defects probably prevented the valve from being "excellent." Thus, over the span of 295,000 cycles, existing cracks or surface defects probably worsened, as an increase in leak-rate was evident from 0 cycles to 295,000 cycles. Still, after 295,000 cycles, this valve is functionally competent for physiologic conditions, where proximal pressure is typically 35 to 50 mmHg.

However, an “excellent” valve like B2-8-T9 (3 freeze-thaw cycles) maintained excellent leak-rate characteristics even until over 500,000 open-close cycles. This excellent performance can be attributed to the valve being in excellent condition prior to any cyclic testing. It is presumed it would take longer for an “excellent” valve to lose competency than for a “good” valve to lose competency. The two sets of cyclic life data (B2-8-T9 and D3-4-T5) demonstrates that valve manufacturing was the main culprit in causing the valve to lose functionality, an aspect that can easily be addressed with commercial manufacturing techniques.

TEST E (BURST PRESSURE) RESULTS

The valve failed in maintaining competency at an applied proximal pressure of 530 ± 10 mmHg. This burst pressure is six times greater than physiologic proximal pressure. Five valves were tested under burst-pressure conditions. Only valves that had demonstrated good or excellent competency were subjected to burst pressure testing. One valve burst at 940 ± 10 mmHg of backpressure, failing by a leaflet tear. The four remaining valve did not incur any visible or significant damage to the leaflets when examined during failure analysis. It is hypothesized that two of the valves failed due to leaflet prolapse or folding. The final two valves failed by circumferential leakage; the PVA "glue" used to fix the valves into the tubes was not sufficiently applied. A leak-path propagated along the circumference of the valve, starting at the proximal end of the valve, and spreading to the distal end (Figure 99 and Figure 101). Although the sample size was not large enough to determine significant difference in burst pressure of 3 versus 5 freeze-cycle valves, it does not appear there is a noticeable advantage in burst pressure capabilities.

Table 23: Burst pressure test results

Cycles	Specimen	Leak-rate	Burst Pressure	Failure Mode
3	B1-8-T9	Excellent	940 ± 10 mmHg	Leaflet tear
3	D1-7-T8	Excellent	740 ± 10 mmHg	Leaflet prolapse
3	B3-8-T9	Good	530 ± 10 mmHg	Leaflet prolapse
5	C4-9-T10	Excellent	860 ± 10 mmHg	66% circumference blowout
5	C1-9-T10	Good	530 ± 10 mmHg	50% circumference blowout

FAILURE ANALYSIS RESULTS

Table 24: Failure analysis results

Cycles	Valve	Leak-rate	Status	Failure Mode
3	B1-8-T9	Excellent	Burst testing	Leaflet tear
3	A3-8-T9	Excellent	Reserved	NA
3	D1-7-T8	Excellent	Burst testing	Leaflet prolapse
3	B2-8-T9	Excellent	Cyclic life testing	None, lasted 508,000 cycles
3	B3-8-T9	Good	Burst testing	Leaflet prolapse
3	A4-8-T9	Bad	Cut for analysis	Surface roughness
3	A1-8-T9	Bad	Cut for analysis	Severe pitting
3	C2-7-T8	Bad	Cut for analysis	Hole in right leaflet
3	D2-7-T8	Bad	Cut for analysis	Hole in right leaflet
3	C1-7-T8	Bad	Cut for analysis	Hole in left leaflet
3	A2-8-T9	Bad	Cut for analysis	Surface roughness

Cycles	Valve	Leak-rate	Status	Failure Mode
5	D1-9-T10	Excellent	Reserved	NA
5	C4-9-T10	Excellent	Burst testing	66% circumference blowout
5	C2-4-T5	Excellent	Cut for analysis	None
5	C1-9-T10	Good	Burst testing	50% circumference blowout
5	B3-9-T10	Good	Cut for analysis	None
5	D3-4-T5	Good	Cyclic life testing	None, lasted 295,000 cycles
5	B1-4-T6	Good	Reserved	NA
5	C1-4-T5	Bad	Reserved	NA
5	A2-4-T6	Bad	Reserved	NA
5	D3-9-T10	Bad	Cut for analysis	Surface roughness
5	D4-9-T10	Bad	Cut for analysis	Surface roughness
5	D2-9-T10	Bad	Cut for analysis	Surface roughness

Figure 91: Comparison of human femoral vein valve afflicted with primary incompetence (top) [22], human femoral vein valve that is normal (middle) [22], and a good prosthetic vein valve fabricated in this research (bottom)

Valve ID	B1-8-T9
Freeze-thaw cycles	3
Leak-rate performance	Excellent
Test history	1) opening pressure 2) reflux pressure 3) opening pressure 4) burst pressure testing
Failure mode	Leaflet tear; valve burst at 940 ± 10 mmHg

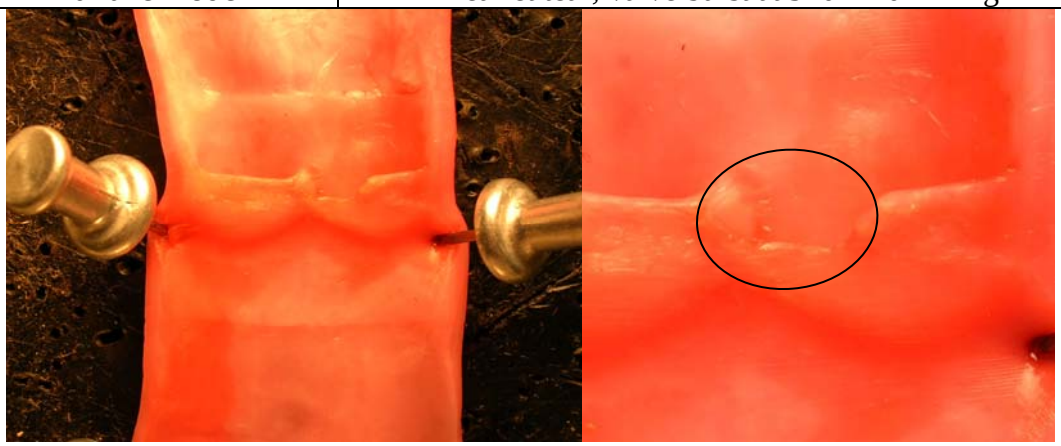


Figure 92: Qualitative failure analysis of valve leaflets (specimen B1-9-T9)

Valve ID	A4-8-T9
Freeze-thaw cycles	3
Leak-rate performance	Bad
Test history	1) opening pressure 2) reflux pressure 3) opening pressure
Failure mode	Leaflet surface roughness

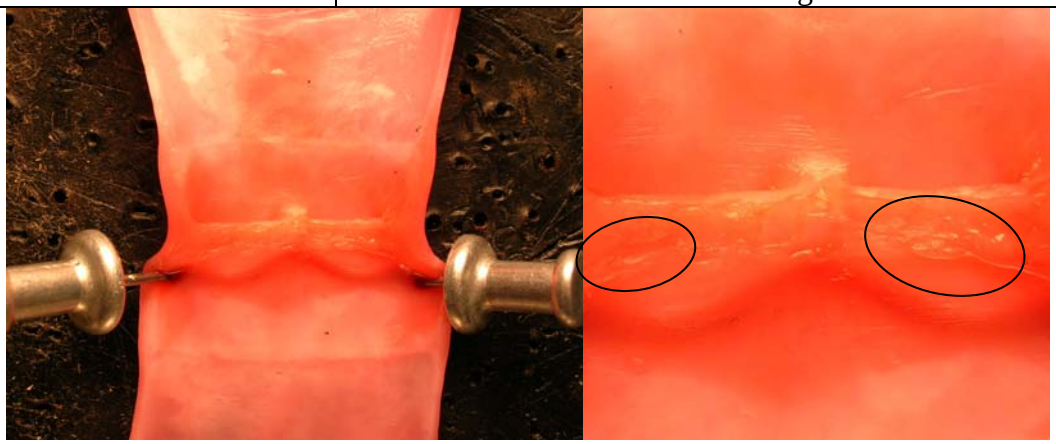


Figure 93: Qualitative failure analysis of valve leaflets (specimen A4-8-T9)

Valve ID	A1-8-T9
Freeze-thaw cycles	3
Leak-rate performance	Bad
Test history	1) opening pressure 2) reflux pressure 3) opening pressure
Failure mode	Leaflet surface roughness

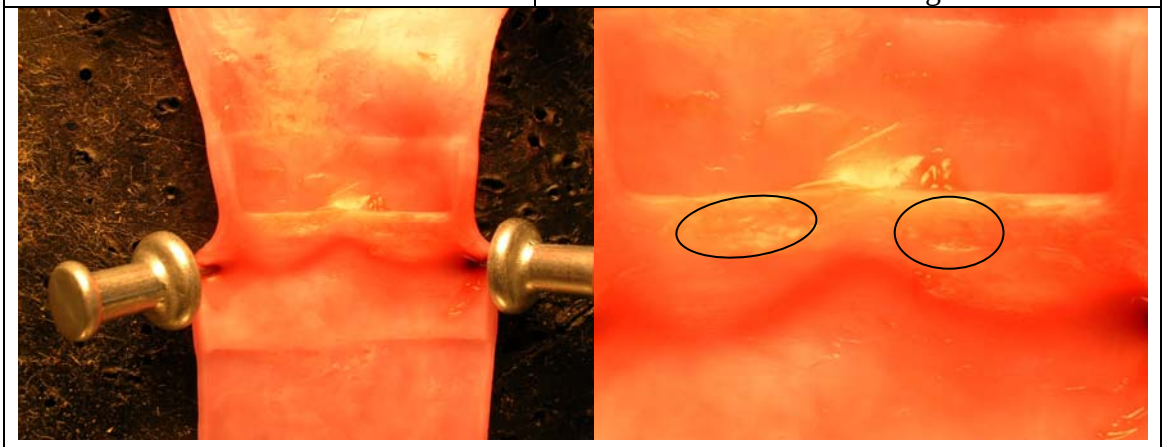


Figure 94: Qualitative failure analysis of valve leaflets (specimen A1-8-T9)

Valve ID	C2-7-T8
Freeze-thaw cycles	3
Leak-rate performance	Bad
Test history	1) opening pressure 2) reflux pressure 3) opening pressure
Failure mode	Leaflet hole, leaflet surface roughness

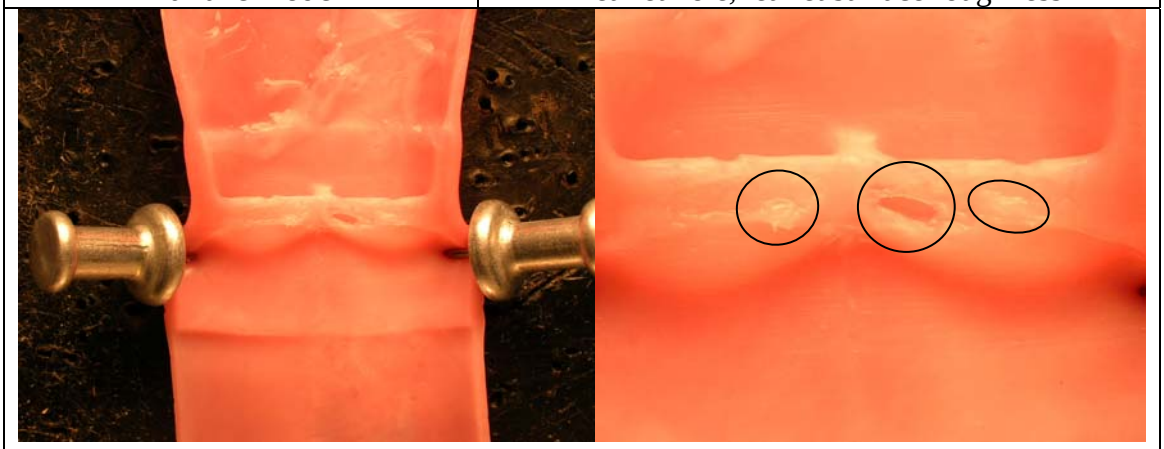


Figure 95: Qualitative failure analysis of valve leaflets (specimen C2-7-T8)

Valve ID	D2-7-T8
Freeze-thaw cycles	3
Leak-rate performance	Bad
Test history	1) opening pressure 2) reflux pressure 3) opening pressure
Failure mode	Leaflet hole

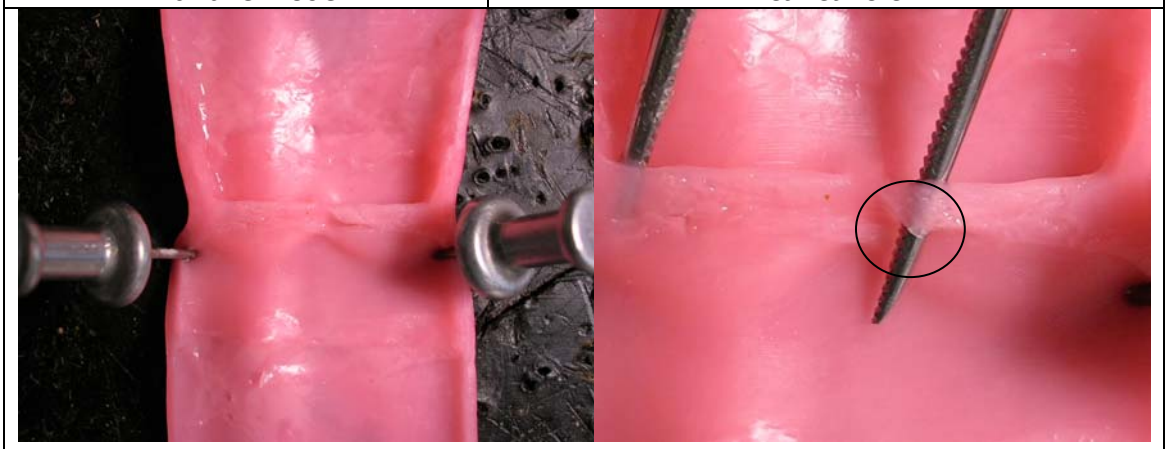


Figure 96: Qualitative failure analysis of valve leaflets (specimen D2-7-T8)

Valve ID	C1-7-T8
Freeze-thaw cycles	3
Leak-rate performance	Bad
Test history	1) opening pressure 2) reflux pressure 3) opening pressure
Failure mode	Leaflet hole

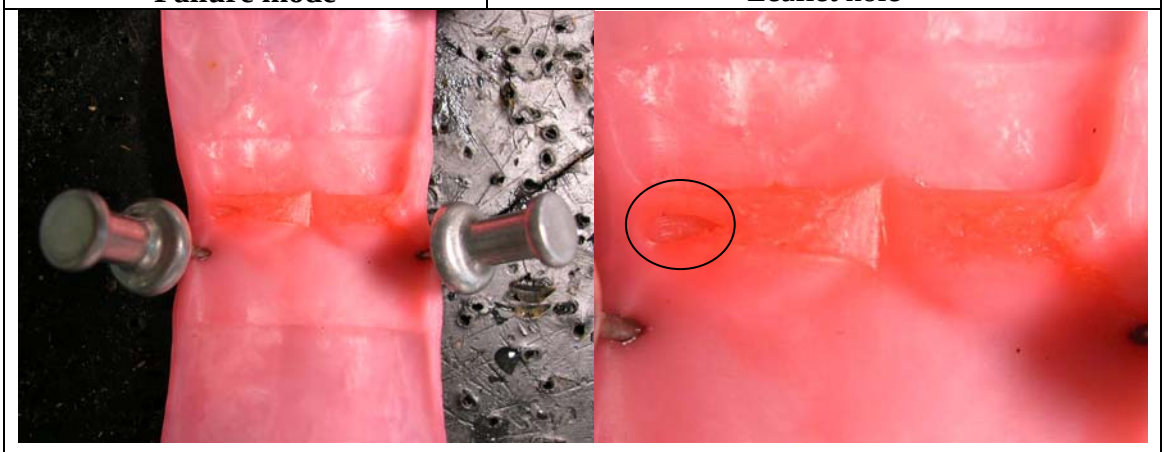


Figure 97: Qualitative failure analysis of valve leaflets (specimen C1-7-T8)

Valve ID	A2-8-T9
Freeze-thaw cycles	3
Leak-rate performance	Bad
Test history	1) opening pressure 2) reflux pressure 3) opening pressure
Failure mode	Leaflet surface roughness (near point of coaption)

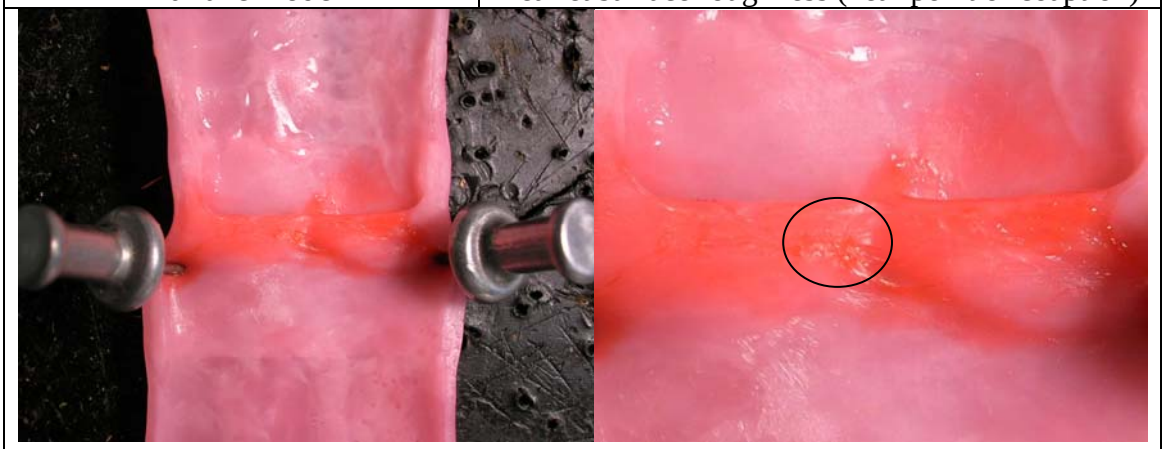


Figure 98: Qualitative failure analysis of valve leaflets (specimen A2-8-T9)

Valve ID	C4-9-T10
Freeze-thaw cycles	5
Leak-rate performance	Excellent
Test history	1) opening pressure 2) reflux pressure 3) opening pressure 4) burst pressure
Failure mode	66% of the circumferential seal was compromised, resulting in circumferential leakage

Figure 99: Qualitative failure analysis of valve leaflets (specimen C4-9-T10)

Valve ID	C2-4-T5
Freeze-thaw cycles	5
Leak-rate performance	Excellent
Test history	1) opening pressure 2) reflux pressure 3) opening pressure
Failure mode	None; the valve is free from holes and has a relatively smooth sealing surface

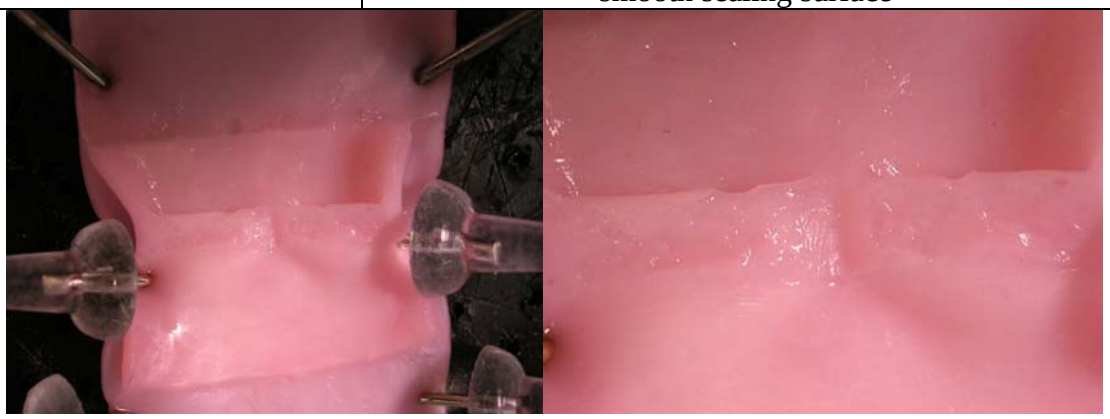


Figure 100: Qualitative failure analysis of valve leaflets (specimen C2-4-T5)

Valve ID	C1-9-T10
Freeze-thaw cycles	5
Leak-rate performance	Good
Test history	1) opening pressure 2) reflux pressure 3) opening pressure 4) burst pressure
Failure mode	50% circumference seal blowout, resulting in circumferential leakage. Leaflets were intact, and sealing surface was relatively smooth.

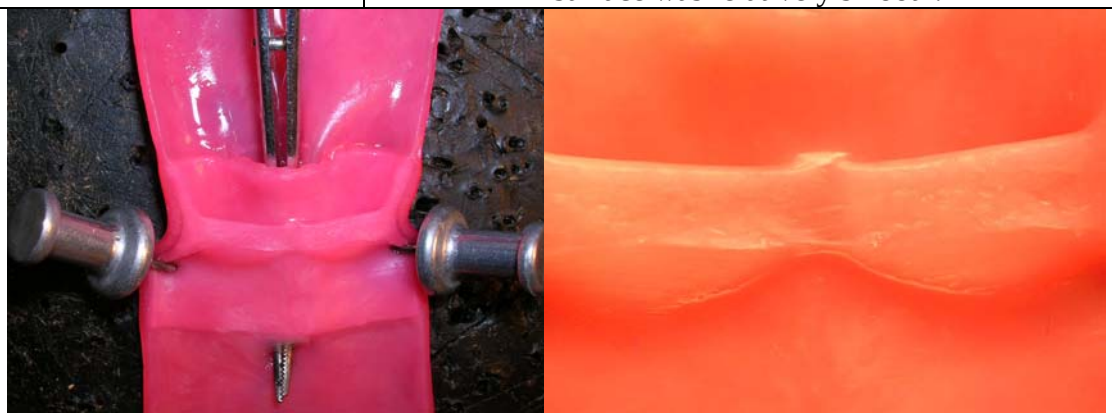


Figure 101: Qualitative failure analysis of valve leaflets (specimen C1-9-T10)

Valve ID	B3-9-T10
Freeze-thaw cycles	5
Leak-rate performance	Good
Test history	1) opening pressure 2) reflux pressure 3) opening pressure
Failure mode	None, but gouge in right leaflet was present. This may attribute to why the leak-rate for this valve throughout proximal testing was equivalent or slightly less than 1.0 mL/min, rather than other good or excellent valves that performed much better.

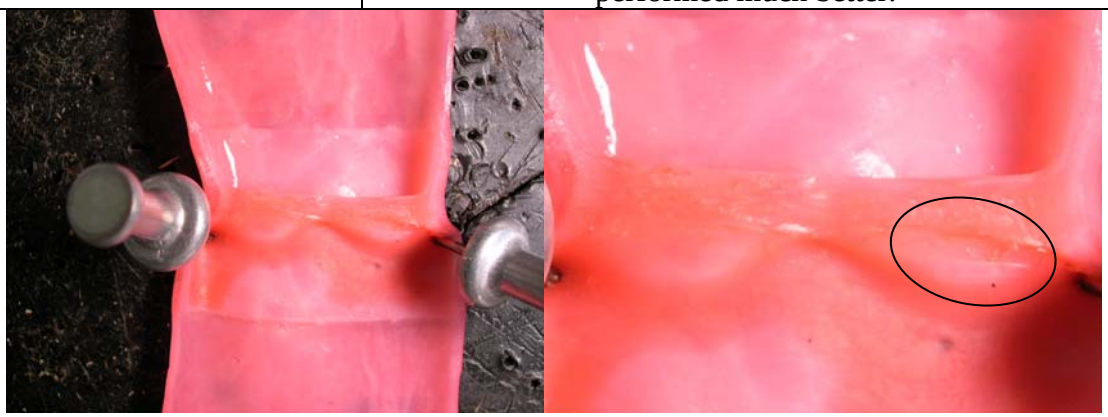


Figure 102: Qualitative failure analysis of valve leaflets (specimen B3-9-T10)

Valve ID	D3-9-T10
Freeze-thaw cycles	5
Leak-rate performance	Bad
Test history	1) opening pressure 2) reflux pressure 3) opening pressure
Failure mode	Leaflet surface roughness – mismatched sealing surfaces

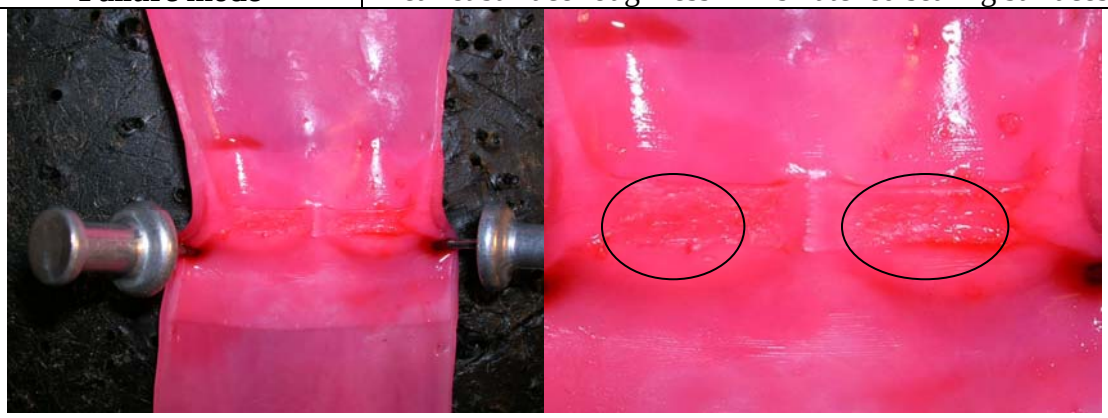


Figure 103: Qualitative failure analysis of valve leaflets (specimen D3-9-T10)

Valve ID	D4-9-T10
Freeze-thaw cycles	5
Leak-rate performance	Bad
Test history	1) opening pressure 2) reflux pressure 3) opening pressure
Failure mode	Leaflet surface roughness – pitting near tube wall

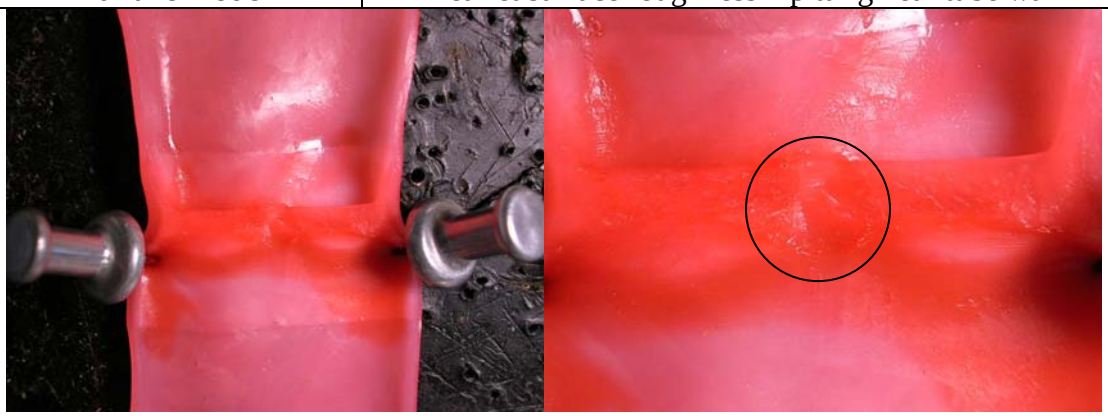


Figure 104: Qualitative failure analysis of valve leaflets (specimen D4-9-T10)

Valve ID	D2-9-T10
Freeze-thaw cycles	5
Leak-rate performance	Bad
Test history	1) opening pressure 2) reflux pressure 3) opening pressure
Failure mode	

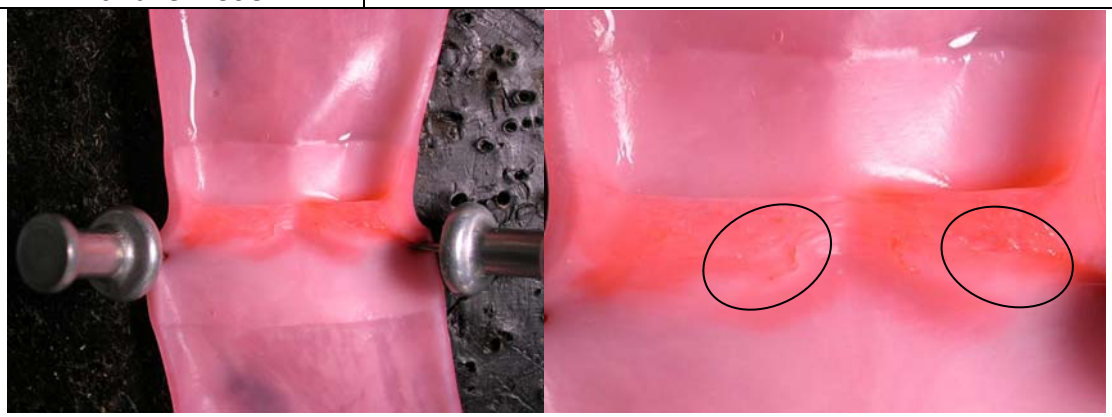


Figure 105: Qualitative failure analysis of valve leaflets (specimen D2-9-T10)

SUMMARY OF RESULTS

The novel prosthetic valve met the three critical design criteria specified earlier in this thesis. The valve opens with a pressure gradient less than 5 mmHg, withstands 300 mmHg of backpressure while having no greater than 1.0 mL leakage per minute, and maintains this functionality even after opening and closing over 500,000 times. The valve failed at a burst pressure of 530 ± 10 mmHg, a pressure six times greater than physiologic proximal pressure. The valve's design concept has demonstrated itself as a clinically relevant functional design.

Of 11 test valves fabricated using 3 freeze-thaw cycles, five showed excellent or good competency results. Valves that demonstrated leak-rate performance meeting the leak-rate design criteria (leak-rate less than or equivalent to 1.0 mL/min) were deemed as "good valves." Valves demonstrating better performance, having leak-rates equivalent to or less than 0.5 mL/min were deemed "excellent valves." Valves exceeding the leak-rate design criteria were labeled as "bad valves." This categorization of valves determined how the valves would be processed for failure analysis after testing.

Amongst the 3 freeze-thaw cycle valves that exhibited good or excellent competency results, the average initial opening pressure was 2.9 ± 1.6 mmHg. The average opening pressure for the valve design increased to 5.1 ± 2 mmHg after being exposed to very high proximal pressure (300 mmHg). The six valves that failed proximal pressure testing underwent failure analysis, and all failures could be attributed to abnormalities in

manufacturing. Abnormalities included torn leaflets, excessive leaflet porosity, and leaflet surface roughness due to incorrect cutting of the leaflet orifice. These abnormalities showed that the valve did not fail because of design aspects, but because of limited manufacturing capabilities in a lab setting (manufacturing success was about 45%). Despite manufacturing limitations, the valve design met all design criteria for opening pressure and reflux leakage. One 3 freeze-thaw cycle valve underwent cyclic testing and continued to be functional after 500,000 cycles of opening and closing.

Of 12 test valves fabricated using 5 freeze-thaw cycles, seven showed excellent or good results. Of these seven valves, the average initial opening pressure was 3.6 ± 2.4 mmHg. The average opening pressure for the valve design increased to 5.7 ± 1.9 mmHg after being exposed to very high proximal pressure (300 mmHg). Failure analysis was performed on three of the valves that failed proximal pressure testing. All three failures could be attributed to abnormalities in manufacturing. Abnormalities involved excessive leaflet surface roughness due to incorrect cutting of the leaflet commissure. Manufacturing success was 58%, evidenced by 7 of 12 valves showing good or excellent proximal pressure performance. One 5 freeze-thaw cycle valve underwent cyclic testing and continued to be functional after 295,000 cycles of opening and closing.

CHAPTER 4

DISCUSSION

ANALYSIS OF TEST RESULTS

Table 25: Comparison of results for prosthetic vein valves involving bench testing

Study	Opening Pressure	Reflux leakrate	Cyclic Life Functionality	Burst Pressure	Valve test environment
DeLaria et al (1993) Bovine valves (gluteraldehyde-fixed and fresh)	Not clearly specified	120 mL/min for fresh valve at 287 mmHg; 40 mL/min for fixed valve at 287 mmHg	Tested in a pulsatile flow loop, but no pressure results reported	Not tested	Vein that the valve resided in experienced some sinus expansion
Hill et al (1985) Pellethane valves	4.5 mmHg	Not tested	Water perfused at 120/80 mmHg at 60 bpm for 47 days – no quantitative test results reported	Not tested	Not specified
Pavncik et al (2001-2003) SIS stented valve	1 mmHg	Withstood 300 mmHg, but no leak-rate reported	Not tested	Not tested	Rigid plastic tube
Taheri et al (1988) Pyrolytic carbon mechanical valves	Not reported	Not reported	After 5 months, no significant damage to mechanical valves	Not tested	Tygon® tubing
Sathe (2006) 3 freeze-thaw cycle valve	**2.9 ± 1.6 mmHg**	**Less than 0.5 mL/min at 300 mmHg**	**Functional after 500,000 cycles**	**530 ± 10 mmHg**	**Vein-like tube with sinus expansion**

Test A: Initial Opening Pressure

The 3 freeze-thaw cycle prosthetic vein valve opened with an average pressure of 2.9 ± 1.6 mmHg, which meets the design criteria for opening pressure. This opening pressure is largely dependent on the elastic modulus of the leaflets, the leaflet angle, and

particularly the leaflet thickness. The leaflet thickness in the valves tested in this research was approximately 0.7 mm, which is rather large compared to the 0.05 mm thickness that most natural human vein valve leaflets have [14]. The 0.7 mm thickness was necessary for manufacturing the valve in a lab setting; thinner leaflets would be more difficult to cut with surgical scissors to create the orifice. However, if the valve were manufactured using expensive equipment with higher precision and accuracy, the valve leaflets could be made much thinner without sacrificing quality. The reduction in leaflet thickness should reduce the opening pressure of the valve. It would be reasonable to expect opening pressures around 1.0 mmHg after refining the valve leaflet thickness, and still maintain valve competency at high proximal pressures.

The Pellethane® valve developed by Hill *et al* opened at a pressure of 4.5 mmHg. However, no data was reported regarding the pressure performance of the valve after subjected to multiple cycles of opening and closing or after subjected to high sustained backpressure. The authors reported problems of patency due to thrombus formation in most of the occluded valves; all Pellethane® valves had occluded within 8 days of surgery.

Compared to prior studies, DeLaria *et al* developed a more comprehensive approach in evaluating a prosthetic vein valve's performance. They examined prosthetic vein valves with a more physiologically relevant flow loop, and conducted reflux leakage testing. They did report opening pressures of 1 mmHg for valves for gluteraldehyde-fixed bovine jugular veins; however, the valve leaflets were fixed in a slightly pre-opened position,

and opening pressure is really not a relevant parameter to measure for a pre-opened valve.

Pavcnik *et al* created a SIS valve that opens with a pressure gradient of 1 mmHg [33]. This valve demonstrated very good opening pressure characteristics in bench testing, and has shown good promise as a prosthetic vein valve. However, the valve seemed sensitive to correct placement and implantation; approximately one-third of valves that were slightly tilted in the vein or placed in tortuous anatomy caused thrombus formation [33, 35]. Excessive thrombus formation often leads to an occluded or incompetent valve. Any type or design of prosthetic valve could be adversely affected by incorrect placement or poor implantation technique. However, a valve can be designed such that its performance is less sensitive to human error or improbable events.

The valve presented in this research has been designed to minimize the potential for skewing in a vein by having a length-diameter ratio close to or greater than 2. When placing these valves into the vein-like tubes for specimen preparation, it was observed that there was very little opportunity for the valve to skew. However, skewing will also be a function of correct sizing for the vein, as well as local expansions in the vein wall. It will be prudent for future work to include delivery and implantation techniques to assess the valve's alignment, placement, and retention.

Test B: Reflux Leakage

The prosthetic valve presented in this research demonstrated the ability to withstand 300 mmHg of applied proximal pressure with leak-rate less than 0.5 mL/min. This is a very good result compared to prior prosthetic valve studies. For example, DeLaria *et al* applied 287 mmHg of proximal pressure on fresh and gluteraldehyde-fixed bovine jugular vein valves, which resulted in 120 mL/min and 40 mL/min reflux leak-rates, respectively [31]. These leak-rates are very high compared to the prosthetic vein valve developed in this research. Also, introducing bovine valves into humans may cause immunogenic responses.

The square-stent SIS vein valve developed by Pavcnik et al demonstrated the ability to withstand 300 mmHg in a rigid plastic tube. However, no leak-rate data was reported, and thus it is difficult to quantitatively assess this valve's competency in high proximal pressure conditions. Also, a rigid plastic tube does not mimic the mechanics and compliance of a human vein as well as a flexible tube. It would be interesting to examine the SIS valve's competency in a dynamic, high proximal pressure environment. The authors did conduct descending venograms of their valve in a sheep model and demonstrated competency, which showed potential of their valve a prosthetic substitute with respect to competency at low proximal pressures. Competency performance at high proximal pressure has not yet been reported.

Hill *et al* and Taheri *et al* did not report conducting tests to examine reflux leakage. Also, while DeLaria *et al* observed sinus expansion in the bovine valves, the other three

studies did not account for the elasticity of natural human veins. An implanted prosthetic valve will be subject to various intramuscular pressures, tortuous anatomy, and dynamic changes in vein diameter. Thus, a prosthetic valve should be tested in an environment that mimics venous function. This involves mimicking venous distention and also sinus expansion. Figure 106 shows that the vein-like tubes used in this research mimicked venous distention behavior, while Figure 107 shows sinus expansion similar to a biologic vein valve.

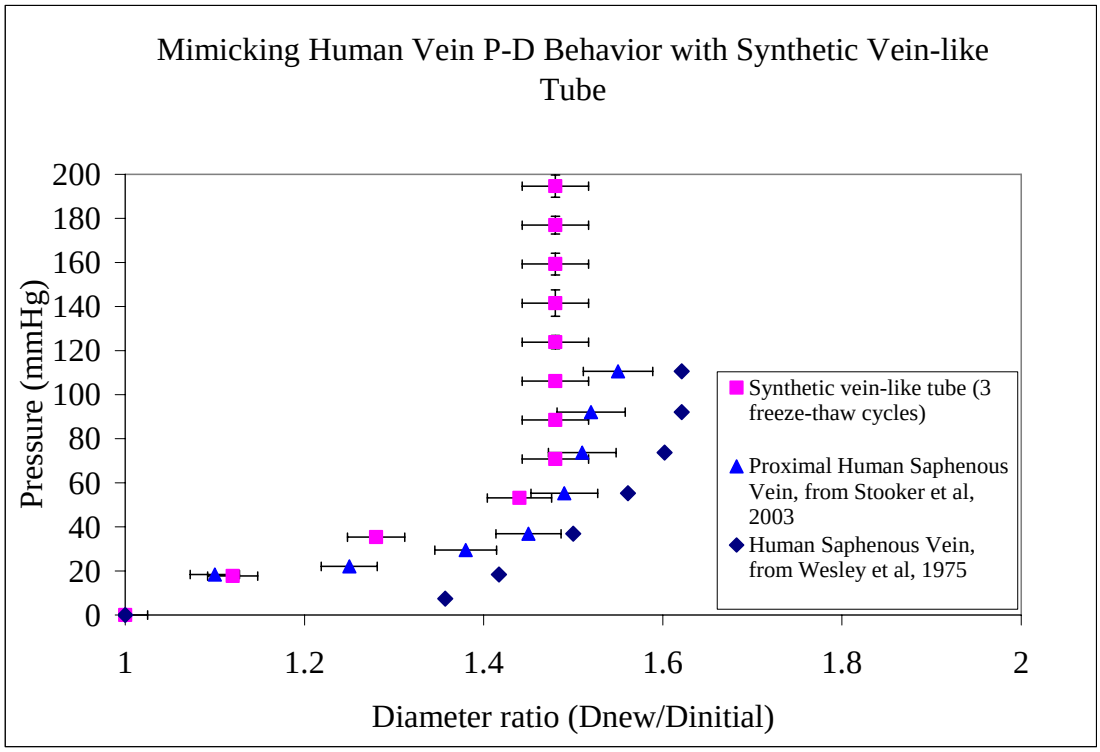


Figure 106: Synthetic vein-like tube for testing valves displayed similar compliance and diameter distention behavior to natural human leg veins. Distension was limited to about 1.5 times the original diameter by the restrictive plastic tube placed around test specimens. This graph was recreated in part using data from Wesley *et al* [12] and Stooker *et al* [13]. No error data was available for Wesley *et al*.

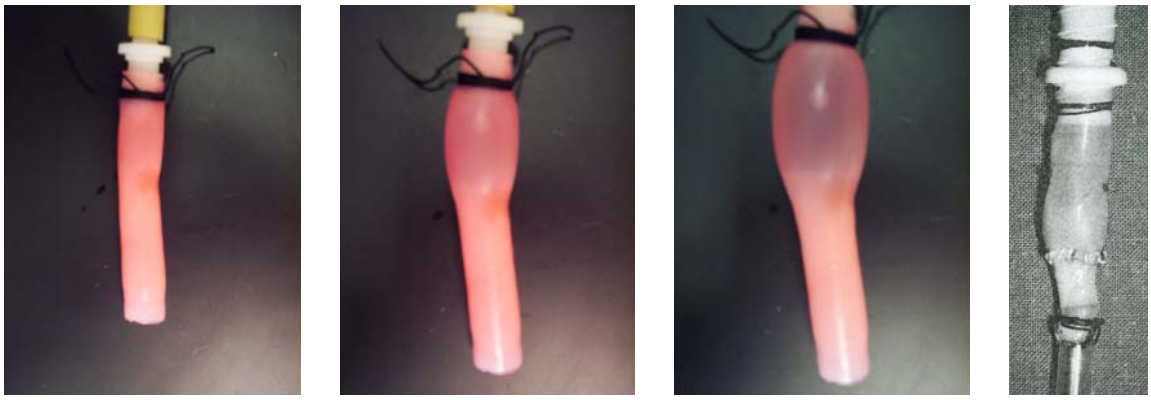


Figure 107: Prosthetic vein valve exposed to back pressures (R-L) : 0 mmHg, 90 mmHg, 170 mmHg, and canine femoral vein valve exposed to 184 mmHg [52] (Far right). Note the similarity in sinus distension between the artificial vein-like tube and the human vein. The vein-like tube simulated vein mechanics with respect to sinus expansion, and provided a more accurate test environment for determining reflux performance than a rigid tube.

Test C: Second Opening Pressure

This test was performed to assess whether the valve's opening pressure characteristics would change after the valve was exposed to high sustained proximal pressures. There was about a 2 mmHg increase (2.9 ± 1.6 mmHg to 5.1 ± 2.0 mmHg) in opening pressure, most probably due to the viscoelastic nature of PVA. Such a test was not performed on prior prosthetic valves, so it is difficult to determine the relative performance of this valve. It is clear that the initial opening pressure (from Test A) meets the design requirements for opening pressure. The second opening pressure (from Test C) is border-line with the design criteria. Although the second opening pressure is a result from exposing the valve to extreme (300 mmHg) proximal pressure, it is nevertheless an area for improvement. The second opening pressure can be lowered by creating leaflets that are thinner, and thus lowering both initial and second opening pressures. Also, testing the valve at physiologic proximal pressures (35 to 50 mmHg) may provide a more

relevant prediction of second opening pressure. Realistically, proximal pressure on the most proximal CFV valve will rarely exceed 120 mmHg for a sustained period of time. Exposing the valve to 300 mmHg and retesting opening pressure may be too aggressive of a test. Regardless however, the second opening pressure of the valve is an important performance attribute of the valve, and work should be done to lower the second opening pressure.

Test D: Cyclic life functionality

This test demonstrated the novel prosthetic valve's functionality at various points of cyclic life testing, including after the valve opened and closed more than 500,000 times. The test was terminated not because of any valve failure (the valve was still in excellent condition) but rather because the pump used in the test setup was beginning to wear. The results indicated that the valve could withstand a reasonable lifespan and remain functioning.

It is difficult to analyze the internal cracking or micro-damage induced on any engineering product in cyclic life testing without using destructive methods. Because the number of valve specimens for testing was limited, destructive methods were not used, and thus data was not available for fatigue damage. The next best method for determining the integrity of the valve was to use functional testing throughout cyclic life testing. It was assumed that a valve that had poor structural integrity would not perform well in the functional tests. This assumption held true, evidenced by identifying gross defects in "bad" valves during failure analysis. However, the failure analysis was a

qualitative assessment of the valve's structural integrity. The next step for failure analysis would be to use quantify the porosity, cracking, and damage using destructive methods.

It was clear from the failure analysis that the leaflets are the region of the valve most susceptible to damage. As the leaflets are the most dynamic part of the valve, they are the attributes of the valve that should be analyzed further for structural integrity during cyclic testing. Areas that may be susceptible to fatigue damage are hypothesized in Figure 108, based on the cyclic dynamics of the valve in those areas. An accurate finite element model may provide a more quantitative assessment of stress and strains in the valve leaflets, as well as information about the effects of crack propagation and accumulated micro-damage on valve performance.

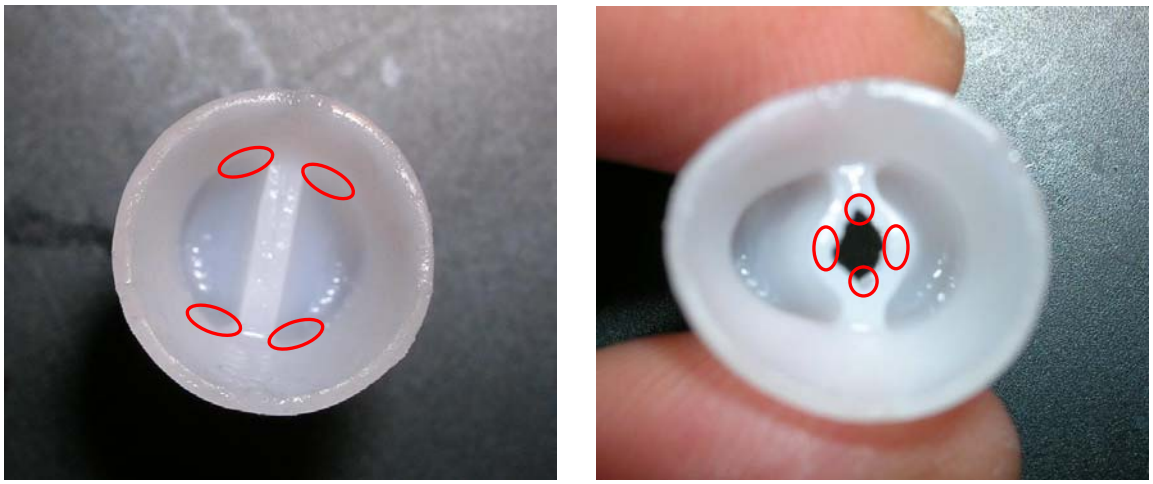


Figure 108: Valve regions potentially susceptible to fatigue damage.

Table 26: Comparison of cyclic flow loop test parameters

Study	Net flow	Cycle Frequency	Stroke Volume	Proximal Pressure	Duration Tested	Valve Integrity
DeLaria *et al* (bovine valves)	670 ± 70 mL/min	0.2 Hz	~ 56 mL	30-45 mmHg	NA	NA
Taheri *et al* (mechanical valves)	300 mL/min	0.27 Hz	~ 19 mL	100 mmHg	5 months	"little or no fatigue"
Sathe	**450 ± 30 mL/min**	**0.7 Hz**	**~ 10 mL**	**50 ± 5 mmHg**	**500,000 cycles**	**Valve demonstrated excellent competency**

Both Taheri *et al* and DeLaria *et al* subjected their prosthetic valve to some sort of cyclic life testing. Taheri *et al* used a phase pump that operated at 16 cycles/min to expose the valve to alternating proximal pressure of 100 mmHg in a flow-loop system [30]. The net flow was 300 mL/min. The platinum and the pyrolitic carbon-covered titanium valves were tested for 5 months. The study reported "little or no fatigue of materials." Metal valves can be expected to have reasonably long life, and demonstrate good cyclic fatigue performance. However, a metallic valve in a venous environment imposes the risk of erosion through the vein, discomfort for the patient, and may cause unnecessary trauma to the vein. The design of the metallic valve was likely an extension of heart valve design. Blood flow in the heart is very different from blood flow in the venous system, and a heart valve may not be suitable for venous applications.

DeLaria *et al* used a respiratory pump that operated 12 cycles/min, and expose their bovine jugular vein valves to proximal pressures ranging between 30 and 45 mmHg [31]. The net flow was 670 ± 70 mL/min. However, beyond placing the valve into a cyclic flow loop, little results were reported on the functionality of the valve during cyclic testing. Also, the time duration of cyclic testing was not specified. In light of this

absence of reported data, it seems that the loop was used more to evaluate the valve opening and closing characteristics during each pump of the calf rather than long term functionality.

Test E: Burst Pressure

To date there has been little work in characterizing the burst pressure of a prosthetic vein valve. This research presents a prosthetic vein valve that withstood at least 530 ± 10 mmHg of proximal pressure before leaking excessively. This burst pressure is about six times greater than physiologic proximal pressure imposed on CFV valves. Improved manufacturing of the valve will probably result in higher burst pressure. In particular, quality issues related to porosity, material homogeneity, and composite structures will become important for future burst testing.

Recommendations for additional testing

This research proposed four test methods for evaluating the functionality of a prosthetic vein valve. Test methods were developed for measuring opening pressure, reflux leakage, cyclic life, and also burst pressure. These tests target the operational functionality of the valve that can expose failure mechanisms. However, there are other tests that could be completed to gain additional insight into the valve's performance. For example, cyclic life testing occurred in physiologic conditions; to accelerate fatigue, cyclic life testing could be conducted with higher proximal pressure. Also, simulating external pressure on the valve will mimic the intramuscular pressures a natural vein valve experiences. This could be accomplished by surrounding the test specimen with a

pressure chamber. Bench testing could also include manipulating and bending the valve to mimic the dynamic loading of a valve in tortuous anatomy.

Bench testing should also evaluate the fixation methods used for the valve. This research used PVA solution to "glue" the valve into the tube specimen. It would be important to study how sutures, stents, or hooks or barbs will affect the performance and functionality of the valve. Implantation and fixation techniques are discussed in the subsequent "Future Work" section. Finally, tests should be created to study the valve's impact on vascular biology. Namely, thombogenecity and immunogenicity of the valve should be studied using an animal trial.

PATENTABILITY

This research presents a new and novel implantable prosthetic vein valve. This is the first flexible prosthetic vein valve having two leaflets that seal with significant surface contact area contained within a tube with a flared inlet and outlet to facilitate circumferential sealing. The valve's leaflets are not pre-opened, are non-parabolic in shape, and meet in surface sealing contact, thus creating a robust sealing mechanism. The valve is flexible, unlike much of prior art describing rigid frameworks and metal struts, and thus will comply with tortuous venous anatomy. It will adapt to the elliptical cross-section of veins, as well as vein distention. The valve will impose minimal radial stress on vein walls compared to prior art describing radially expanding stiff valves.

A provisional patent application has been filed with the U.S. Patent and Trademark Office (GTRC ID 3471). This invention has the freedom to operate in a commercial setting. There is no knowledge of infringement of prior art at the time this thesis is published. Table 27 provides a comparison of the Sathe *et al* invention to the more similar prior art, demonstrating that the Sathe *et al* invention does not infringe on prior art.

Table 27: Sathe *et al* valve does not infringe on prior art

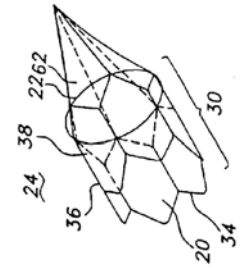
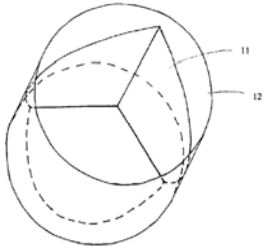
Patent # and Inventor	**Date Issue**	**Title + Description**	**Main Claims**	**Main differences with Sathe *et al* valve**	**Diagram from patent filing**
6,840,957 DiMatteo *et al*	01/11/05	**Implantable prosthetic valve** Radially expanding, contains wire scaffold with leaflets composed of polymeric fibers, bovine pericardial tissue – multiple leaflet design (3 to 8) – specified to hold up to 100 mmHg, open between 1 and 20 mmHg	Generally cylindrical radially collapsible scaffold supporting collapsible leaf valves portion, with leaves constructed of metal frame and sealing lining. Lining to be constructed of polymers, silk, or bovine pericardial tissue. Valve leaves are flexibly hinged	- **metal framework for leaflets** - **valve leaflets contact each other with abutting edges as opposed to area contact** - valve cusps have "open construction frame" with impermeable lining	
6,716,241 Wilder *et al*	04/06/04	**Venous valve and graft combination** Three parabolic sections forming a trileaflet design. Leaflets are attached inside a tube graft, and are suggested to be made of woven fibers, either warp or weft configuration, such as those knit types used in PET arterial grafts	Synthetic, biocompatible material, with inner tube and outer tube, with inner tube forming three equivalent parabolic lobes that interface	- **Three or more cusps** - **inner and outer tube assembly** - Cusps are approximately **parabolic** - **tube is straight**, has no flaring to accommodate venous distention	

Table 27 (continued)

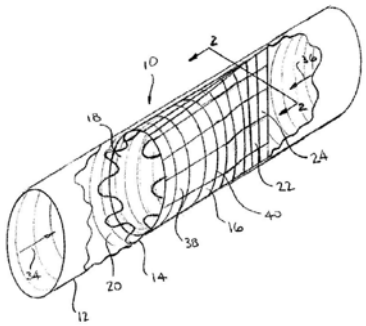
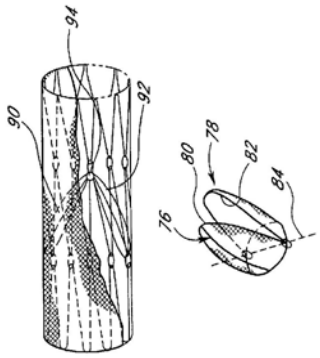
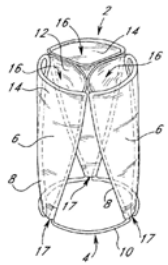
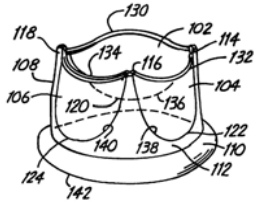
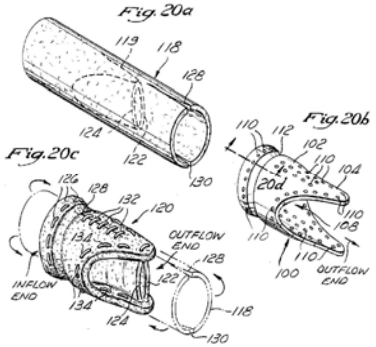
Patent # and Inventor	Date Issue	Title + Description	Main Claims	Main differences with Sathe *et al* valve	Diagram from patent filing
6,494,909 Greenhalgh	12/17/02	**Endovascular valve** Plurality of leaflets (patent prefers two), formed within a tube of braided flexible filaments. Leaflets made of flexible material (does not specify). For higher pressure applications, patent suggests intermeshing longitudinal supports into the leaflets	One-way valve having flexible tube formed of intermeshed filaments, collapsible within a catheter, formed into plurality of leaflets, with means of flexibly biasing leaflets together. Leaflets made of flexible membrane comprised of silicone layer.	- Tube formed of **braided intermeshed** filaments - membranes composed of silicone layer - radial supports on both ends - elongated supports	
6,299,637 Shaolian *et al*	10/09/01	**Transluminally implantable venous valve** Self-expanding wire-structure, containing at least one leaflet (diagram depicts bileaflet design), preferably two, with valve cusps composed of a "duckbilled" shape	Self-expandable vein valve with tubular metal wire support, containing at least two longitudinal struts, structured around at least one leaflet, with leaflets having wire frame and two eyelets, allowing leaflet to pivot to open and close.	**- leaflet pivots on two points** of contact formed by **metal wire** loop eyelets - leaflet has internal support - **tubular metal wire frame** supports polymeric sleeve	
6,287,334 Moll *et al*	09/11/01	**Device for regulating the flow of blood through the blood system** Tubular wire frame with shape memory alloy metal, containing several pockets (valve sinuses) for valve cusps	A support frame configured to press outwards against vein wall, having at least one collapsible flow restriction pocket. The support frame is generally tubular, and collapsible for catheter implantation.	- **metal wire support frame** - generally **conical** shaped cusp pockets	

Table 27 (continued)

Patent # and Inventor	Date Issue	Title + Description	Main Claims	Main differences with Sathe *et al* valve	Diagram from patent filing
6,562,069 Cai *et al*	05/13/03	**Polymer leaflet designs for medical devices** Flexible polymer leaflets connected to supporting ring and commissure protrusions – trileaflet design – **St. Jude Medical**	Rigid stent support structure and plurality of flexible polymer leaflets and commissural supports. Polymer material selected from group of polyurethanes, silicones, and a few others (no hydrogels mentioned)	- **no tubular construct or housing** - **valve area in relaxed state is open** at least 10 percent of luminal area - **rigid support structure** (not flexible) with scallops - at least **three** leaflets	
5,824,061 Quijano *et al*	10/20/98	**Vascular and venous valve implant prostheses** Exovascular support device, acts like template in aiding implantation and transplantation of venous valves, also acts as dilation restrictor when implanted around vessel body (from Baxter, Inc)	Vascular system for facilitating implantation of vascular graft, containing tubular exovascular stent, dilation restrictor with flanges to fit over the vessel. Endovascular venous valve prosthesis contains stent assembly, preserved vein segment, suture apertures for facilitating surgery.	- **chemically preserved vein segment** containing a valve - exovascular stent support for facilitating surgical implantation of preserved valve - stent contains suture template for attachment of valve to vein	

FUTURE WORK

Design refinement

Some improvements can be made to the valve's leaflets, namely creating thinner leaflets for improved opening pressure performance. However, thinner leaflets may pose more of a problem with cyclic life functionality or competency at high proximal pressures. A compromise must be found, where opening pressure can be lowered without sacrificing competency or cyclic life. Finite element modeling and further experimentation will be helpful to optimize leaflet thickness. Also, the valve material could be made into a composite to help prevent accumulation of micro-damage, propagation of cracks, or cracking. Interspersed filaments, fibers, or meshes may improve the long term structural integrity of the valve. It is important to note that the valve leaflets need not be the same thickness of natural vein valves to be functional. Mechanical heart valves look nothing like natural heart valves, yet still remain functional as a treatment for heart valve pathologies. Similarly, a vein valve design can have leaflets that may be different from natural vein valves, provided that the prosthetic vein valve affords the same functionality as a native vein valve.

Design for manufacturing

There are a few design features that could be improved to help facilitate a high-yield manufacturing process. The leaflets are the most complex feature of the valve, and will require accurate manufacturing processes to ensure good valve performance. The design

worked well with injection molding during prototype development. However, there were some problems with air bubbles becoming trapped in tight geometrical spaces. The valve design should be adapted to include drafts and improved fillet radii to facilitate better flow of material during injection molding.

If metal molds are to be used rather than silicone molds, then the metal molds will probably have to be machined. The rough mold shape can be cast; however, special machining processes will be required to create small design features and angles in the metal mold. Most likely, ball-end milling will be used to create the cavity molds. This may require alterations in angles and curvatures, particularly in the valve pocket regions to allow the tool bit to fit into tight spaces. There is some freedom in the design to allow the valve to be altered in shape to accommodate manufacturing needs. The primary goal of the design is to remain operationally function, and there are various combinations of geometry changes that can be made while still attaining functionality.

Improved manufacturing techniques for high production yields

Precise manufacturing processes will greatly benefit the valve's performance. As this research has shown, the design concept works well. Valves that had failed could be attributed to poor manufacturing techniques that caused leaflet tears, holes, or excessive leaflet surface roughness. Thus, improved manufacturing should eliminate a majority of these failures, resulting in valves that perform consistently well. The cutting of the orifice is a process that caused most variability in valve quality. An alternative to cutting the commissural opening could be to use precision laser cutting. A laser with a small

spot size will cut the leaflets in a non-contact manner, thus minimizing cutting variability associated with material elasticity. A high-quality CO_2 laser can cut a minimum width of 100 to 150 microns, to a depth of several millimeters. However, laser cutting the leaflets will not be an easy process to control. Also, pressure testing would have to be conducted to determine if this gap in the leaflets would be acceptable to prevent reflux leakage. A second alternative to create a good orifice is to create it in the molding process. The molds could incorporate a thin rigid film to ace as a separator to keep the leaflets from binding against each other during valve curing. However, the thin film or foil must be robust enough to withstand many molding cycles.

The molds in this research were created of silicone for their low cost, ease for manufacturing, and transparency. However, in a high yield manufacturing environment, the molds must be made such that dimensional tolerances will be small to reduce variability in the process. Typically for medical device manufacturing, stainless steel is used for tooling because it will maintain its dimensions for a reasonable time period, and does not corrode easily. High-quality machined stainless steel molds should be created for high-yield manufacturing.

At some point, the manufacturing process should yield sterile, packaged valves. This will be necessary to make prototypes for use in pre-clinical animal trials, and eventual human trials. Sterilization of the valves will require adjustments in manufacturing tooling, processes, and quality control. It is not easy to sterilize PVA, since a steam autoclave will melt the material, and a gas-plasma oxidizer will dehydrate the material. Rinsing the

PVA valve in a chemical bath could be a sterilization option; however, residual chemicals should be removed prior to packaging, since certain chemicals may be toxic.

Design for implantation

While this research has focuses on designing a functional valve from an operational perspective, the valve must eventually be configured for implantation into human veins. This is a necessary step to help translate this technology from an engineering laboratory to a hospital operation room. There are three modes of implantation that have been envisioned for this prosthetic valve. The first involves a standard longitudinal venotomy of the affected vein, through which the valve can be inserted and pushed proximal of the venotomy by 1 or 2 cm. The valve can then be fixed into place using 6-0 or 7-0 vicryl non-absorbable interrupted sutures. However, the sutures will be blind, and thus subject to potential error. To help combat these human factors, improvements should be made to the design to facilitated implantation. For example, a slightly raised ring could be placed around the flared inlet and outlet of the valve, for the surgeon to feel through the vein wall. This ring could serve as an anchor for sutures. Or, the valve could incorporate a radiopaque tag or marker, or could be radio-luminescent so that the surgeon can visualize the valve using a fluoroscope.

A second method for implanting the valve could be to conduct a standard transverse venotomy, severing the afflicted vein into two tubes. The valve could be implanted to create an end-to-end anastamoses with the distal and proximal ends of the vein. Suture placement would not be blind, and the surgeon could better affix the valve into place. To

facilitate this end-to-end anastamoses implantion, the valve body could be designed to be longer to accommodate the resection of damaged vein walls. The valve inlet and outlet could incorporate a Dacron® ring to facilitate neointimal sealing of the proximal and distal vein segments to the valve.

The third method for implanting the valve would involve a more minimally invasive approach: catheter delivery. This prosthetic valve is very flexible and is resistant to kinking, and can be packaged inside a catheter. The catheter could access a distal vein branch of the afflicted vein, and thus could deliver the valve to the desired site. There are several methods for fixing a catheter-delivered valve into place. The first is using a balloon-expandable stent that is incorporated into the cylindrical body of the valve. A self-expanding stent can also be used. A third fixation method involves using hooks or barbs that are embedded in the valve's body. The hooks or barbs will catch into the vein wall, and will prevent the valve from migrating. This fixation method is often used to keep a vena caval filter in place, so that it can continue to trap embolic debris in patients. However, issues of vein trauma should be examined - cyclic loading and pressurization of the valve may cause the hooks or barbs to tear the vein wall.

Pre-clinical animal trial

The valve has demonstrated functional performance in bench testing; the next phase of functional testing should involve a pre-clinical animal trial. A short term feasibility study has been planned and submitted for IACUC (Institutional Animal Care and Use Committee) review to evaluate the valve's thrombogencity and patency in a porcine

model. Other animal models for future consideration could include ovine and canine models. Good results from an animal trial could pave the path to eventual clinical studies and device clearance in Europe and the U.S. for human clinical use.

CHAPTER 5

CONCLUSIONS

This research defined key design specifications for a prosthetic vein valve to be considered functionally operational. It was determined that the valve should 1) open with a pressure gradient less than 5 mmHg, withstand 300 mmHg of backpressure while having no greater than 1.0 mL leakage per minute, and maintain this functionality even after opening and closing over 500,000 times. These design specifications were developed after examining consumer needs and focusing on the more critical operational requirements that would dictate the performance of the valve.

This research developed physiologically relevant test methods for quantifying the operational functionality of a prosthetic vein valve. Each test was designed to demonstrate the valve's performance with respect to the design specifications. Test A (initial opening pressure) and Test C (second opening pressure) demonstrated the patency of the valve for design criteria 1. Test B (reflux leakage testing) and Test E (burst pressure testing) evaluated the competency of the valve for design criteria 2. Test D (cyclic life testing) showed the valve's functionality after numerous cycles of operation. Failure analysis then assessed structural quality of the valves, and linked any failures to distinct and identifiable problems from manufacturing. The design of the valve was not an issue in valve failures.

The valve's design concept has proven itself as a functional design via functional testing. The novel prosthetic valve met the three aforementioned critical design criteria. The valve can open with a pressure gradient as low as 2.6 ± 0.7 mmHg (Specimen B1-8-T9). The valve can withstand 300 mmHg with a leak-rate less than 0.5 mL/min. The valve can withstand over 500,000 cycles and still meet the design criteria for opening pressure and reflux leakage. The valve design failed at a burst pressure of 530 ± 10 mmHg, a pressure six times greater than physiologic proximal pressure. The valve presented in this research is operationally functional, and shows good potential as a solution to treating deep valvular incompetence in CVI patients.

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